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GRANT NUMBER DAMD17-98-1-8238

TITLE: Post-Mastectomy and Phantom Breast Pain: Risk Factors, Natural History, and Impact on Quality of Life

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REPORT DATE: July 1999

TYPE OF REPORT: Annual

PREPARED FOR: Commanding General
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY *(Leave blank)*	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	July 1999	Annual (1 Jul 98 - 30 Jun 99)

4. TITLE AND SUBTITLE
Post-Mastectomy and Phantom Breast Pain: Risk Factors, Natural History, and Impact on Quality of Life

5. FUNDING NUMBERS
DAMD17-98-1-8238

6. AUTHOR(S)
Robert H. Dworkin, Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of Rochester
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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*

Post-mastectomy pain syndrome (PMPS) and phantom breast pain are poorly understood chronic pain syndromes that occur following surgical procedures for breast cancer. Although these pain syndromes are not well studied, there is appreciable evidence that patients with PMPS or phantom breast pain can be significantly disabled by their chronic pain and can suffer from substantial reductions in quality of life. The primary aims of this research project are to identify risk factors for these chronic pain syndromes following surgical procedures for breast cancer, characterize their natural history, and examine their impact on quality of life using a prospective research design. To date, 40 women scheduled for surgical procedures for breast cancer have been assessed with respect to hypothesized risk factors for chronic pain. These women are now being studied for one year following their surgery, with periodic assessments of pain, health-related quality of life, and psychosocial variables. This allows risk factors for PMPS and phantom breast pain to be identified and the impact of chronic pain on quality of life to be determined. The pathogenesis of PMPS and phantom breast pain are unknown, and the identification of risk factors constitutes an important first step in understanding the processes by which chronic pain develops; this knowledge may lead to the development of more effective treatment approaches. By identifying risk factors, the results can also be used to design interventions aimed at preventing the development of chronic pain following surgical procedures for breast cancer. Moreover, the identification of risk factors will make it possible to determine which patients are most in need of such preventive efforts.

14. SUBJECT TERMS
Breast Cancer
Chronic Pain; Post-Mastectomy Pain Syndrome; Phantom Breast Pain

15. NUMBER OF PAGES
50

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

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Introduction

Post-mastectomy pain syndrome (PMPS) and phantom breast pain are poorly understood chronic pain syndromes that occur following surgical procedures for breast cancer. The primary aims of this research are to identify risk factors for these chronic pain syndromes following surgical procedures for breast cancer, characterize their natural history, and examine their impact on quality of life using a prospective research design. Women scheduled for mastectomy, lumpectomy, or excisional biopsy are being assessed with respect to hypothesized risk factors for PMPS and phantom breast pain and are then being studied prospectively for one year. Periodic follow-up assessments of pain, health-related disability and quality of life, and selected psychosocial variables will allow risk factors to be identified and the impact of chronic pain on quality of life to be determined. An important feature of this research is its detailed assessment of pre-operative, early post-operative, and chronic pain; in these assessments, sensory and affective aspects of pain, pain quality, and non-painful abnormal sensations are being examined. By identifying risk factors for chronic pain following surgical procedures for breast cancer, the results of this research can be used to design interventions aimed at preventing the development of these chronic pain syndromes.

Body of Annual Report

Chronic pain has been defined as pain that persists beyond the normal time of healing, a definition which includes most painful conditions that have lasted longer than three months (Merskey & Bogduk, 1994). Chronic pain is both a medical and a behavioral problem and it is accompanied by substantial economic costs to society as well as great personal suffering. The current research is a prospective study of the development of post-mastectomy pain syndrome (PMPS) and phantom breast pain. Neither of these two chronic pain syndromes has been well studied. It has been suggested that PMPS is caused by surgical injury to the intercostobrachial nerve (Foley, 1987; Vecht et al., 1989; Stevens et al., 1995; cf. Watson et al., 1989, who noted that in some patients the cutaneous branches of other intercostal nerves are also involved). The pathophysiology of phantom breast pain—as well as other phantom pains—remains obscure (Katz & Melzack, 1990; Melzack, 1990, 1996; Sherman, 1997). In a recent review, most reports of the prevalence of PMPS were within the range of 16% to approximately 50% (Kwekkeboom, 1996). Not included in this review were two recent studies of PMPS in which 39% of 181 patients reported pain at least one year after surgery (Wallace et al., 1996) and 20% of 95 patients reported "chronic, stable pain of long duration" beginning within days to weeks after surgery (Stevens et al., 1995, p. 63). Early studies of phantom breast pain (excluding non-painful phantom breast sensations) reported prevalences ranging from 18-54% (Jamison et al., 1979), and a recent study found phantom breast pain present in 13% of patients three weeks and one year after mastectomy and in 17% of patients at six years (Krøner, 1989, 1992). Although the prevalence of PMPS and phantom breast pain might be expected to decrease with duration of time since surgery, the results of several studies indicate that this may not occur (Krøner et al., 1989, 1992; Vecht et al., 1989; Maunsell et al., 1993). It has been suggested that women are often reluctant to report pain following mastectomy to their physicians, which may contribute not only to the impression that pain following mastectomy is rare but also to the variability in the results of studies of the prevalence of PMPS and phantom breast pain (Jamison et al., 1979, Abraham & Llewellyn-Jones, 1983; Staps et al., 1985). Importantly, both PMPS and phantom breast pain have

been found to have a significant negative impact on psychological adjustment, the performance of daily occupational and domestic activities, and quality of life (e.g., Jamison et al., 1979; Christensen et al., 1982; Hladiuk et al., 1992; Maunsell et al., 1993; Stevens et al., 1995).

Very few studies have examined risk factors for pain following mastectomy, and no consistent relationships have emerged between the likelihood of persisting pain and age, type of mastectomy, cancer treatment, or post-operative sequelae (Jamison et al., 1979; Christensen et al., 1982; Krøner et al., 1989, 1992). In one recent study, women with pre-mastectomy breast pain were more likely to have phantom breast pain three weeks, one year, and six years after surgery than those without pre-mastectomy pain (Krøner et al., 1989, 1992). The results of studies of limb amputees are consistent with this finding (Jensen et al., 1985; Katz & Melzack, 1990; Weiss & Lindell, 1996). The results of these studies suggest that patients with pain before either a mastectomy or a limb amputation are at greater risk for the development of phantom pain. Moreover, the risk appears greatest for patients with more severe pain, and it has been hypothesized that phantom pain may develop when the combination of pre-amputation pain intensity and duration exceeds a critical threshold (Katz & Melzack, 1990).

The presence of psychosocial distress in patients with pain following mastectomy has been interpreted as evidence that psychosocial factors contribute to the development of pain (Woods, 1975; Jamison et al., 1979; Christensen et al., 1982). However, psychosocial distress can be a consequence of living with prolonged pain, and the absence of prospective studies has made it impossible to determine whether psychological abnormalities in patients following mastectomy and limb amputation are risk factors that preceded the development of chronic pain or are consequences of it (Sherman et al., 1987; Katz, 1992). Nevertheless, there is evidence that stress can precede increases in phantom pain (Arena et al., 1990), and the results of prospective studies suggest that psychosocial factors can be risk factors for other pain syndromes (Dworkin, 1997a) as well as for pain associated with cancer treatment (Syrjala & Chapko, 1995). It is therefore important to determine whether patients who have greater psychosocial distress before surgical procedures for breast cancer are more likely to develop PMPS or phantom breast pain.

The theoretical approach on which this research is based is one in which the development of chronic pain is considered the result of an interaction between biological and psychosocial processes. The principal investigator and his colleagues have proposed that the results of chronic pain research are consistent with a diathesis-stress model (e.g., Dworkin & Portenoy, 1996; Dworkin & Banks, 1999). In this approach, an interaction between an organic condition (the diathesis) and various psychosocial factors (the stress component of the model) is hypothesized to account for the development of chronic pain. The diathesis-stress approach provides a heuristic model that can be used in the design of research on the development of chronic pain following mastectomy. In such a model, a mastectomy or lumpectomy and the nerve damage associated with these procedures can be considered the diathesis for chronic pain; various psychosocial factors constitute the stress (broadly defined) that results in a process whereby acute peri-operative pain becomes the chronic pain of PMPS and phantom breast pain.

The prospective study of mastectomy and lumpectomy patients has the potential to identify risk factors derived from this model for the development of chronic pain following surgical procedures

for breast cancer. To identify risk factors, patients with pain at a 3-month follow-up interview are considered to have chronic pain (Merskey & Bogduk, 1994). Patients who do and do not develop chronic pain will be compared with respect to each of the measures in five families of variables assessed pre-operatively—demographic and medical/surgical, acute pain, health-related disability, psychological distress, and social support and life events. Because the results of cross-sectional studies that have attempted to identify risk factors for PMPS and phantom breast pain within the demographic and medical/surgical domain have been inconsistent, it is hypothesized that there will be no significant risk factors within these families of variables. As reviewed in Dworkin (1997a), the results of a number of studies indicate that more severe acute pain and greater psychosocial distress are risk factors for the development of chronic pain. It is therefore hypothesized that acute pain intensity and duration and measures within the two families of psychosocial variables will be significant risk factors for both PMPS and phantom breast pain.

A second aim of this research is to examine the psychosocial consequences of chronic pain following surgical procedures for breast cancer. It has been proposed that the assessment of chronic pain patients should be multidimensional (Turk & Rudy, 1987; Dworkin, 1997b). This approach has been used as a basis for selecting measures of the impact of chronic pain on psychological distress and quality of life. It is hypothesized that psychological distress, maladaptive illness beliefs, and health-related physical, role, and social disability will increase in patients with persisting chronic pain from the 3-month follow up through the final follow-up assessment at 12 months.

Methods

English-speaking women 18 years of age and older scheduled for mastectomy, lumpectomy, or excisional biopsy are being recruited from the surgical service at Strong Memorial Hospital (SMH). The inclusion of patients scheduled for lumpectomy and excisional biopsy represents a modification to the original research protocol. This change was made based on the increasing reliance of surgeons on these more conservative surgical procedures for the treatment of early stage breast cancer. Approval for this modification was obtained from the U.S. Army Medical Research and Materiel Command and from the University of Rochester Research Subjects Review Board.

Women scheduled for breast surgery at SMH whose names and telephone numbers are released by their attending surgeon are being contacted and the study is described to them over the telephone. Those who agree to participate have their pre-operative assessment scheduled within two weeks of their surgery. At this assessment, the patient is asked to sign an informed consent form. A project coordinator or a research nurse conducts subject recruitment and the pre-operative assessments. Most of these assessments are conducted in patients' homes to facilitate their participation. Some assessments are conducted at SMH, if the patient so desires or if it is deemed unsafe for the research personnel to visit the patient's home. Patients are reimbursed $80 for participation in the research in two installments—$40 at the conclusion of the pre-operative assessment, and $40 upon completion of the 12-month follow-up interview. To date, 40 women have been enrolled in the research, have had their pre-operative assessment, and are undergoing follow-up assessments. This constitutes successful progress with respect to the accomplishment of Tasks 1, 2, 5, and 6 in the approved Statement of Work.

Post-operative pain and analgesic use are being assessed in hospital visits or telephone interviews at 2 and 10 days after surgery; this will make it possible to examine the relationships between acute post-operative pain and analgesic equivalence levels (Steedman et al., 1992) and the development of PMPS and phantom breast pain. At 1, 3, 7, and 12 months following surgery, telephone interviews are being conducted in which mastectomy-related pain and disability, analgesic use, health status and treatment history since the previous assessment are assessed. Surgery-related pain at the 3, 7, and 12 month follow-up interviews will be considered chronic pain (Merskey & Bogduk, 1994). The criteria of Watson et al. (1992) will be used to diagnose PMPS and the criteria of Krøner et al. (1989, 1992) will be used to diagnose phantom breast sensations and phantom breast pain. Use of these criteria will ensure that PMPS and phantom breast pain are distinguished from other types of pain that may be present at these follow-up interviews, including radiation plexopathy and neuritis (e.g., Watson & Evans, 1982; Watson et al., 1989) and post-mastectomy scar pain (e.g., Krøner et al., 1989, 1992).

To examine whether persisting pain is accompanied by increasing psychosocial distress, the questionnaire measures of depression, anxiety, disease conviction, and somatization are also administered during the follow-up interviews. These interviews are conducted by a member of the research team who did not conduct the initial assessments, who is therefore blind with respect to the patient's pre-operative psychological status. Because the identities of patients who do and do not develop pain will only become known at the follow-up interviews, the project coordinator conducting the pre-operative assessments will be blind with respect to the data used to identify risk factors for chronic pain.

Measures

Demographic and medical/surgical measures. Basic demographic data—age, race, marital status, number of children, living arrangements, years of education, occupation, and current employment status—are assessed at the beginning of the pre-operative assessment. The subject's medical history is assessed by means of an expanded version of the physical health section of the Life Stressors and Social Resources Inventory (see below; Moos & Moos, 1994). Information regarding past and current illnesses and treatments, including past and current painful conditions (based on the methods of S.F. Dworkin et al., 1990), is obtained from this interview.

Information regarding the patient's breast cancer history, type of mastectomy, and degree of sparing of the intercostobrachial nerve is obtained from the attending surgeon and operative report. The type and duration of operative and post-operative anesthesia and analgesia will be recorded from the patient's hospital records. Information regarding the dosage and portal of entry of any radiation treatment following surgery will be obtained from the patient's radiation oncologist. At the present time, collection of this information on the subjects presently enrolled in the research (Tasks 3 and 4 in the approved Statement of Work) has been delayed. This is due to the fact that many of the enrolled patients are undergoing continuing medical and radiation treatment. For this reason, collection of these data has been delayed until these treatments are complete or until the patient has finished her last follow-up visit.

Pre-operative pain, early post-operative pain, and chronic pain. Comprehensive assessments of pre-operative pain, early post-operative pain, PMPS, and phantom breast pain are being conducted

using the Brief Pain Inventory Short-form (BPI; Cleeland & Syrjala, 1992) and the McGill Pain Questionnaire (MPQ; Melzack, 1975); the reliability and validity of both measures has been extensively documented. The BPI was developed specifically for use in assessing cancer pain, and the MPQ provides an assessment of both sensory and affective aspects of pain, as well as providing a characterization of pain quality. No previous studies of PMPS and phantom breast pain have distinguished the sensory and affective aspects of pain, a central component of current pain research (e.g., Fernandez & Turk, 1992; Chapman, 1993), nor have pain quality and abnormal but non-painful sensations in these syndromes been carefully assessed. Indeed, in some studes of phantom breast pain, painful and non-painful phantom breast sensations have not been clearly distinguished (e.g., Christensen et al., 1982; Karydas et al., 1986).

Many amputees describe phantom limb pain "as indistinguishable from the pain they experienced in the limb prior to amputation" (Katz, 1992, p. 282), and the MPQ will also be used to examine the hypothesis that the quality of any pre-mastectomy pain and the quality of PMPS and phantom breast pain are similar. In addition, administering the MPQ will make it possible to examine whether the predominant qualities of phantom breast pain remain the same in the year following surgery, as has been reported by Krøner et al. (1989).

Health-related disability, quality of life, and psychological distress. At the pre-operative assessment, patients are administered the Medical Outcomes Study short-form health survey (SF-36; Ware et al., 1992) as well as the Functional Assessment of Cancer Therapy-Breast (FACT-B; Brady et al, 1997). The SF-36 will provide measures of health-related physical, role, and social disability in the week immediately prior to surgery. The impact of post-mastectomy pain on quality of life at each of the follow-up interviews is assessed by readministering the FACT-B at the 1, 3, 7 and 12 month follow-up assessments.

Depression and anxiety have been found to be risk factors for chronic pain as well as consequences of chronic pain (Banks & Kerns, 1996; Dworkin, 1997a), and measures of both are administered at the pre-operative assessment and at the 1, 3, 7, and 12 month follow-up interviews. The Hamilton rating scales for depression and anxiety (Hamilton, 1959, 1960) is administered at the pre-operative assessment using structured interviews developed for these measures (Williams, 1988, unpublished manual). To complement these interview-based assessments, two self-report measures of symptoms of depression and anxiety are also administered—the Beck Depression Inventory (Beck et al., 1961), a measure of depression that has been used in a large number of studies of chronic pain, and the State-Trait Anxiety Inventory, state version (Spielberger, 1977), a measure of the extent to which an individual feels anxious at the present time. The combined use of these interviews and questionnaires provides an assessment of the moderately severe forms of depression and anxiety that appear to be both risk factors for and consequences of chronic pain.

Several measures that reflect the individual's beliefs about physical illness and somatic symptoms are also administered at both the pre-operative assessment and at the 1, 3, 7, and 12 month follow-up interviews. These are the Illness Behavior Questionnaire disease conviction scale (Pilowsky, 1989), the Somatosensory Amplification Scale (Barsky et al., 1990), and the Somatic Symptom Inventory (Barsky et al., 1990). As reviewed in Dworkin et al. (1996), these measures have been reported to have important relationships with chronic pain in both cross-sectional and prospective studies. Their

administration will make it possible to evaluate whether maladaptive beliefs about relationships between physical symptoms and illness and heightened awareness of physical symptoms are risk factors for or consequences of pain following mastectomy.

Social support and life events. Moos (1992) has argued that social supports and life events are closely interrrelated and influence each other over time, and that an integrated approach to their assessment is therefore necessary. It has also been noted that whereas most existing measures of life events have focused on temporally discrete events, many psychological and physical disorders may be more closely associated with ongoing chronic stressors (e.g., Monroe & Roberts, 1990; Moos, 1992). Based on these considerations, Moos and his colleagues (Moos, 1992; Moos & Moos, 1994) developed a measure—the Life Stressors and Social Resources Inventory (LISRES)—that has been used in a variety of populations to provide an integrated assessment of chronic stressors, discrete life events, and social supports. The LISRES is administered at the pre-operative assessment to test the hypothesis that decreased social support and stressful life events are risk factors for the development of PMPS and phantom breast pain following mastectomy.

Key Research Accomplishments

- 40 patients have been enrolled and are currently actively participating in the research protocol.
- No patients have withdrawn from participation in the study.
- Computer-scannable data collection forms have been prepared that ensure accurate data entry and minimize the amount of effort required for data verification.
- These accomplishments constitute successful progress with respect to Tasks 1, 2, 5, 6, and 7 described in the approved Statement of Work.

Reportable Outcomes

Because recruitment of subjects and collection of data are ongoing, and analyses of the data have not yet been conducted, there are no reportable outcomes associated with this research at the present time.

Conclusions

Because recruitment of subjects and collection of data are ongoing, and analyses of the data have not yet been conducted, no conclusions from this research can be drawn at the present time.

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Which Individuals With Acute Pain Are Most Likely to Develop a Chronic Pain Syndrome?

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Recent prospective studies of risk factors for the development of chronic pain in individuals with acute pain are reviewed. Particular attention is paid to the finding that severe acute pain is a risk factor for three chronic pain syndromes: phantom pain, postherpetic neuralgia, and chronic back pain. Biomedical and psychosocial risk factors for these chronic pain syndromes have also been identified, and a model is proposed of the relationships between these risk factors and acute pain severity. The implications of these risk factors for designing interventions to prevent the development of chronic pain are discussed, and directions for future research are identified. **Key words:** *chronic pain, acute pain, risk factors, phantom pain, postherpetic neuralgia, back pain*

A fundamental goal of research on chronic pain is to identify which individuals with acute pain develop chronic pain syndromes. This question has important theoretical and clinical implications. Knowledge of the characteristics of individuals who have an increased risk of developing chronic pain has the potential to guide research on the pathogenesis of chronic pain. In addition, knowledge of these risk factors could be used in the design of interventions to prevent chronic pain. The development of preventive interventions with demonstrated efficacy and their subsequent application would lead to major reductions in physical and occupational disability, psychological distress, and health care utilization. Finally, the identification of individuals with an increased risk of developing chronic pain would make it possible to deliver interventions to those who are most in need of preventive efforts.

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Prospective studies must be conducted to determine which individuals with acute pain are most likely to develop chronic pain. Although demanding of time and resources, a prospective research design is necessary because studies of patients who are already suffering from chronic pain and its deleterious effects cannot differentiate antecedents of chronic pain from its consequences. The confounding of potential antecedents of chronic pain with its negative consequences is most obvious in considering psychological factors. For example, it has frequently been reported that a substantial number of chronic pain patients suffer from depression [6,25]; studies of depression in chronic pain patients, however, cannot resolve whether depression is a risk factor for chronic pain or whether the stress of living with chronic pain causes patients to become depressed.

Although studying patients before the onset of chronic pain was at one time considered "an obviously impractical task" [88], several authors have recently discussed prospective research methods for examining the processes by which chronic pain develops in patients with acute pain. Naliboff and Cohen recommended that longitudinal studies should be conducted of groups at high risk for developing pain, including, for example, patients undergoing amputations and patients with acute herpes zoster [72]. Similarly, Flor et al. noted that longitudinal studies of acute pain patients would resolve whether stress is a cause or a consequence of chronic pain [33], and Bruehl and Carlson suggested that antecedents of reflex sympathetic dystrophy could be identified in prospective studies of patients who had sustained traumatic orthopedic injuries [14].

During the past several years, a number of studies have been reported in which risk factors for the development of chronic pain have been identified in three groups of patients with acute pain.* In this research, patients undergoing amputations, patients with acute herpes zoster, and patients with acute back pain have been studied until they could be diagnosed with a

chronic pain syndrome, specifically, phantom pain, postherpetic neuralgia, and chronic back pain.

In this article, the results of these studies are reviewed. Particular attention is paid to the finding that severe acute pain is a risk factor for each of these three chronic pain syndromes. Biomedical and psychosocial risk factors for these pain syndromes have also been examined, and a model of the relationships between these risk factors and acute pain severity is proposed. Finally, the implications of these risk factors for designing interventions to prevent the development of chronic pain are discussed, and directions for future research are identified.

SEVERE ACUTE PAIN IS A MAJOR RISK FACTOR FOR CHRONIC PAIN

Because the distinction between acute and chronic pain is based on pain duration, all chronic pain patients, by definition, have suffered from an episode of acute pain that did not resolve. The presence of acute pain, therefore, places a person at risk for chronic pain. Of course, most individuals who have acute pain do not develop chronic pain; consequently, the characteristics of acute pain patients who do (and do not) develop a chronic pain syndrome must be identified.

In examining which individuals with acute pain are most likely to develop chronic pain, an obvious place to begin is to examine the severity of the acute pain. With respect to patients undergoing amputations, phantom limb pain was reported to be significantly more likely to develop when the duration of preamputation limb pain was longer than 1 month [50]. Unfortunately, preamputation pain intensity was not assessed in this study; however, the investigators noted that patients who required narcotic medications before their amputations were more likely to develop persistent phantom pain than patients who had not received these medications, and they suggested that this finding might reflect greater preamputation pain intensity in the patients with phantom limb pain [50]. In other reports, more severe pains before amputation (e.g., gangrene, thrombosis) were associated with more severe phantom limb pain and appeared to be experienced with greater frequency in patients with phantom pain than were milder preamputation pains (e.g., ingrown toenail, callus) [55,97]. In addition, in women who have had mastectomies, those with premastectomy breast pain were more likely to develop phantom breast pain than those without premastectomy pain [58].

The results of these studies suggest that patients with pain before a limb amputation or mastectomy are at greater risk for the development of phantom pain. Moreover, the risk appears to be greatest for patients with more severe pain, and it has been hypothesized that phantom pain may develop when the combination of preamputation pain intensity and duration exceeds a critical threshold [55].

With respect to acute herpes zoster, it has been recognized for many years that the risk of persisting pain, that is, postherpetic neuralgia (PHN), increases with advancing age [27]. But there are also a considerable number of studies, most quite recent, in which it has been found that herpes zoster patients with more severe acute pain are at greater risk for the development of PHN and for more prolonged pain (when pain is evaluated as a continuum of total pain duration) [5,8,15,22,24,26,31,44,60,67,71,82,98,104]. The majority of these studies have examined the persistence of pain over a 6-month follow-up period, but greater acute pain has even been reported to predict PHN 9 years after acute zoster [67].

A variety of research designs, pain measures, and approaches to examining persisting pain have been used in these studies of herpes zoster, and several have significant methodologic shortcomings. Nevertheless, the results are remarkably consistent, and a relationship between greater severity of acute pain in herpes zoster and greater risk of chronic pain can now be considered an established finding.

Disabling back pain is prevalent in industrialized nations, and it is therefore surprising that relatively few prospective studies of patients with acute back pain have been conducted. In both of two studies of individuals with a first episode of acute back pain, greater acute pain intensity predicted chronic back pain at a 6-month follow-up visit [75,102]. In a study of patients visiting a general practitioner for a first or new episode of back pain, a set of measures of the history and severity of previous and present low back pain predicted pain and disability 2 and 12 months later [56]. Unfortunately, it is not possible to determine from the report of this study whether previous or present acute back pain severity or both predicted low back pain and disability at the follow-up evaluations.

In other recent studies of patients with an acute low back pain episode, greater acute pain and disability predicted which patients at 6-month [40] and 1-year [41] follow-up visits were disabled and had not returned to work because of their original back injury. Acute pain and disability were examined as a single variable in these studies, and it is therefore unclear whether greater acute pain or greater acute disability or both increased the risk of developing chronic low back pain.

* Risk factors for chronic pain in patients with acute pain, which have been termed secondary predictors, have been distinguished from risk factors for chronic pain in healthy individuals (primary predictors) and risk factors for treatment outcome in chronic pain patients (tertiary predictors) [40,77].

The results of other studies, however, suggest that greater acute pain and greater acute disability each increase the likelihood that an individual with acute back pain will develop chronic pain [75,102].

The results of the studies reviewed in this section provide considerable support for the conclusion that greater acute pain severity differentiates patients with acute pain who develop chronic pain from patients whose episode of acute pain resolves. Because there are few studies of phantom pain in which the role of acute pain severity has been examined, this conclusion derives most of its support from studies of herpes zoster and acute back pain. It is important, however, to recognize that the results of research on the role of central neuroplasticity in the pathophysiology of pain are also consistent with the conclusion that more severe acute pain—and the greater afferent barrage that accompanies it—increases the likelihood that pain will persist [7,18,28,51,105].

SENSORY AND AFFECTIVE/COGNITIVE ASPECTS OF ACUTE PAIN

In view of these findings, one important goal for future research on the development of chronic pain should be to determine which specific aspects of acute pain predict which specific aspects of chronic pain. By providing a more detailed characterization of risk factors and outcomes, such information may lead to greater accuracy in identifying those acute pain patients who are most likely to develop chronic pain. In such studies, it will be important to examine the distinction between the sensory and the affective and cognitive components of pain, a fundamental feature of current theory and research on pain [17,29,30,42,43,70,79,80]. In research examining this distinction, the sensory qualities of pain (e.g., throbbing, sharp, burning) and the affective/cognitive aspects of pain (e.g., unpleasant, distressing, miserable) are considered integral components of an individual's response to pain that should be assessed separately. Only two of the prospective studies reviewed above, however, distinguished sensory from affective/cognitive components of acute pain in examining the relationship between acute pain severity and the development of chronic pain; in those studies, acute sensory and affective pain each significantly predicted PHN [24] and chronic back pain [75].

In future studies, it will also be important to examine specific qualities of acute and chronic sensory pain. This will make it possible to determine whether the quality of pain remains constant in individuals with acute pain who develop chronic pain and whether specific qualities of acute sensory pain identify those who are most likely to develop chronic pain. The qualities of preamputation pain and phantom limb pain are similar in many patients [50–52,55]; indeed, "many amputees describe the pain in the phantom limb as indistinguishable from the pain they experienced in the limb prior to amputation" [51]. Although the results of one study suggest that the qualities of phantom limb pain may change within the first year following amputation [50], the predominant qualities of phantom limb pain appear to persist for many years. Knifelike pain was reported by 55% of patients with phantom limb pain 8 days after surgery [50] and by 65% of patients an average of 7 years after surgery [57]. The predominant qualities of phantom breast pain—knifelike and other "exteroceptive" pains—also appear to remain the same during the first year following mastectomy [58]. Unfortunately, these studies have not examined whether the patients who are most likely to develop phantom pain are those who suffer from knifelike pain before their amputation or mastectomy.

Similarly, none of the studies that have reported a relationship between the severity of acute herpes zoster pain and the development of PHN have examined whether certain types of acute pain are more likely to persist than others. Burning pain is more common in patients with PHN than in patients with acute herpes zoster, who are more likely to report sharp, stabbing pain [9,13]. Based on these results, it can be hypothesized that acute herpes zoster patients with burning pain are at greater risk for the development of PHN. Interestingly, the results of a recent study suggested that PHN patients who had been treated with acyclovir (an antiviral agent that inhibits varicella-zoster virus replication) during their acute infection were much less likely to report burning pain than PHN patients who had not received acyclovir; reports of throbbing pain in these two groups did not differ [12,13]. Although steady, intermittent, and allodynic pains have been distinguished in research on PHN [84,95], the results of this study indicate that it will be essential to examine four different types of pain—steady throbbing pain, steady burning pain, intermittent sharp or shooting pain, and allodynia—in future research investigating the relationship between the sensory qualities of acute herpes zoster pain and the development of PHN.

The quality of acute sensory pain has not been examined in prospective studies of acute back pain, perhaps because psychosocial factors are often thought to play an overriding role in the development of chronic back pain. As will be discussed below, however, distinguishing the sensory and affective/cognitive aspects of acute pain may provide a method for investigating the role played by psychosocial factors in the development of chronic pain.

BIOMEDICAL RISK FACTORS

Greater acute pain severity is not the only risk factor for chronic pain in individuals with acute pain. Various

biomedical risk factors that putatively reflect pathophysiologic processes contributing to acute pain and the development of chronic pain have also been investigated. In considering the results of these studies, it is important to recognize that the assessment of biomedical findings in pain patients involves complex measurement issues that have not been adequately addressed until recently [85,86,89].

Five biomedical risk factors for prolonged pain have been identified in acute herpes zoster patients. These are greater severity of cutaneous signs [22,48, 49,98–100,103], greater sensory dysfunction in the affected dermatome [15,60,73,74], greater magnitude and duration of humoral and cell-mediated immune responses [20,48,49], presence of a painful prodrome [8], and fever greater than 38°C [99]. All of these risk factors can be considered aspects of a more severe acute infection; together, they suggest that greater neural damage during acute herpes zoster contributes prominently to the development of PHN [27].

Although pain radiating to the legs has been reported to be a risk factor for chronic low back pain [10,46], biomedical findings do not appear to play a major role in predicting which patients with acute back pain will develop chronic pain [37,63]. In several recent prospective studies, measures of physical pathology did not make a significant contribution to the prediction of chronic low back pain [16,40,41,102]. Physical factors may, however, predict surgical outcome in back pain patients, but it is beyond the scope of this article to review such studies [45].

The role of biomedical risk factors has not been evaluated in prospective studies of the development of phantom limb pain. As discussed above, greater preamputation pain severity appears to be a risk factor for phantom pain. This finding would be consistent with the possibility that greater preamputation physical pathology—resulting from more severe wounds, for example [55]—is a risk factor for phantom pain.

PSYCHOSOCIAL RISK FACTORS

Various psychosocial factors, including psychiatric disorders, certain personality traits, lack of social support, and stressful life events, have been hypothesized to contribute to the development of chronic pain [21,38,39,66]. Such psychosocial risk factors have been examined in recent studies of patients with acute pain, and the results suggest that psychosocial factors can be antecedents of chronic pain.

In prospective studies of acute back pain patients, greater anxiety [75,102], greater depression [102], presence of a Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R) [1] Axis II personality disorder [40], elevated scores on the Minnesota Multiphasic Personality Inventory (MMPI) hysteria scale [40,41], passive-avoidant coping [96], maladaptive pain cognitions [75], job dissatisfaction [16,102], and being unmarried [59] have been found to predict the development of chronic back pain. In general practice patients with acute low back pain, a set of measures hypothesized to reflect fear-avoidance beliefs and behavior—stressful life events, heightened somatic concern, history of previous severe pain, and passive pain coping strategies—were found to contribute to predicting pain and disability 2 and 12 months later [56]. Unfortunately, it is not possible to determine from the report of this study whether each of these diverse measures contributed significantly to predicting chronic pain.

Depression and several other psychiatric disorders are prevalent in patients with chronic pain [23,25], but it has remained unclear whether these disorders precede or follow the development of chronic pain [6,21,39]. Anxiety disorders and alcohol and substance abuse have been reported to precede the development of chronic low back pain, whereas major depressive disorder appears to occur either before or after the development of chronic low back pain [3,78]. These are important findings, but it has been noted that because they are based on retrospective-recall methods, these results must be confirmed in prospective research [39]. In two such studies, the presence of a DSM-III-R Axis II personality disorder was found to predict chronic low back pain disability in acute back pain patients at a 6-month [40] but not at a 1-year [41] follow-up visit; however, DSM-III-R Axis I disorders, such as major depressive and anxiety disorders, did not predict the development of chronic pain at either follow-up period [40,41]. Gatchel and colleagues have suggested that the results of these studies indicate that major psychopathology is not associated with an increased risk of developing chronic low back pain but that personality disorders may reflect psychosocial vulnerabilities or deficits in coping skills that are antecedents of chronic pain [39,41].

Measures of psychosocial distress, including depression and disease conviction, have also been found to predict the development of PHN in two prospective studies of acute herpes zoster patients [24,26]. The contribution of psychosocial factors to the development of phantom pain, however, has not been examined prospectively. It has been noted that psychosocial distress can be a consequence of phantom pain but that no data have been reported that suggest distress is a risk factor for phantom pain [51,87]. Nevertheless, there is evidence that stress precedes increases in phantom pain in some patients [2], as well as increases in other types of chronic pain [107], and it would therefore be worthwhile to determine whether patients who have greater psychosocial distress before their amputation are more likely to develop phantom pain [52].

The results of several prospective studies of other chronic pain syndromes and of the onset of acute pain provide additional support for the conclusion that psychosocial factors, especially symptoms of depression, can be risk factors for the development of pain [11,35,61,65,76,90,92].

A MODEL OF THE ROLE OF ACUTE PAIN IN THE DEVELOPMENT OF CHRONIC PAIN

The results of the studies reviewed above suggest that acute pain patients with more severe acute pain, greater physical pathology, and greater psychosocial distress are at increased risk for the development of chronic pain. Several of the findings were based on single studies and must therefore be replicated; nevertheless, the results of these studies of phantom pain, PHN, and chronic back pain are important and can serve as a foundation for the design of future studies of these and other chronic pain syndromes.

The results of this research establish severe acute pain as a major risk factor for chronic pain. Unfortunately, the studies that have identified this risk factor for chronic pain have not addressed the processes by which severe acute pain predisposes to the development of chronic pain. As discussed above, an individual's experience of pain has both sensory and affective/cognitive components. Together, the severity and qualities of acute sensory and affective/cognitive pain constitute the individual's overall experience of acute pain. It can be proposed that the severity and qualities of acute sensory pain reflect the severity and nature of the underlying pathophysiologic processes and that the severity and qualities of acute affective/cognitive pain reflect the severity and nature of any psychosocial antecedents. The Figure presents a model of the development of chronic pain in which these relationships between pathophysiologic processes, psychosocial antecedents, and the sensory and affective/cognitive components of acute pain are depicted (the left side of the Figure).

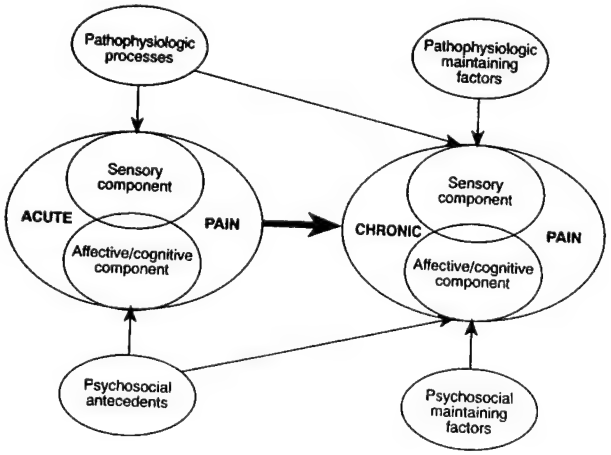

Figure. Model of the role of acute pain in the development of chronic pain.

The research reviewed above indicates that chronic pain is more likely to develop when an individual's overall experience of acute pain is more severe. In the proposed model, biomedical and psychosocial risk factors contribute to the development of chronic pain by determining the severity of the sensory and affective/cognitive components of acute pain. An explanation for why severe acute pain is more likely to persist may be provided by recent theory and research on phantom pain. The results of studies of patients with phantom pain suggest that pain can occur in the absence of any ongoing pathophysiologic [68,69] or psychosocial inputs [51,52,55]. As Melzack has proposed [68,69], if these inputs do not account for phantom pain in these patients, then an explanation for their pain must be sought in central processes (i.e., neural networks in the brain underlying pain and other sensory experiences).† It is likely that such central processes also contribute to the experience of pain in patients in whom pathophysiologic and psychosocial processes do play a role [52,68]. It can therefore be proposed that experiences of severe acute pain are accompanied by prolonged central representations of pain that can persist independently of the pathophysiologic and psychosocial determinants of the acute pain experience.

Pathophysiologic processes and psychosocial antecedents may also make a direct contribution to the development of chronic pain, one that is not mediated by a contribution to acute pain (e.g., factors that impede or promote the resolution of acute pain but that play no role in the experience of acute pain). This is represented in the Figure by the arrows connecting pathophysiologic processes and psychosocial antecedents directly to chronic pain. In addition, as can be seen from the right side of the Figure, other pathophysiologic and psychosocial factors may contribute to the maintenance of chronic pain once it has been established. Diverse factors have been implicated in the maintenance of chronic pain [6,39,93]. Indeed, some of these maintaining factors may be consequences of severe acute pain, for example, depression secondary to pain (such pathways have not been indicated in the Figure).

†The recent finding that magnitude of phantom limb pain and amount of cortical reorganization are highly correlated has been interpreted as consistent with this hypothesis [34].

A few of the findings discussed above suggest that the specific sensory qualities of acute pain can persist, continuing to be experienced when pain has become chronic. Persistence of pain quality does not always occur, however, and the absence of arrows in the Figure connecting the sensory and affective/cognitive components of acute pain with the respective components of chronic pain is intended to emphasize that it is the overall experience of severe acute pain that has been identified as a major risk factor for chronic pain.

It is important to emphasize that the proposed model is an oversimplification. For example, given the relationships between sensory and affective/cognitive pain [30,43,52,55,80], it is likely that pathophysiologic processes and psychosocial antecedents are both associated with each of these two components of acute pain. In addition, protective ("buffering") factors that may reduce the risk of chronic pain are not included in the model [19]. It also must be recognized that the relative contributions of pathophysiologic processes and psychosocial antecedents to acute pain and the development of chronic pain undoubtedly differ for different chronic pain syndromes. For example, pathophysiologic processes appear to play a greater role in the development of PHN than in the development of chronic back pain, in which psychosocial antecedents appear predominant.

It has been proposed that the severity of acute pain reflects its sensory and affective/cognitive components and that these are determined by pathophysiologic processes and psychosocial antecedents. Severe acute pain may then be considered a "final common pathway" by means of which pathophysiologic processes and psychosocial distress jointly contribute to the development of chronic pain. From the perspective of this model, it would be important to determine whether the strength of a relationship between acute pain severity and the development of chronic pain is reduced after controlling for both biomedical and psychosocial risk factors. Unfortunately, only a handful of prospective studies have examined more than one of these three types of risk factors in predicting the development of chronic pain, and such an analysis has not been reported. In these studies, acute pain severity and various psychosocial antecedents were reported to be independent risk factors for chronic pain in patients with acute low back pain [40,41,102] and herpes zoster [24,26]. Only one study examined both psychosocial and biomedical risk factors and acute pain severity, and it was found that greater acute pain and psychosocial distress significantly predicted chronic low back pain but that orthopedic findings did not [102].

Prospective multivariate research designs are necessary to determine whether the pathophysiologic and psychosocial processes that contribute to acute pain account for the relationship between severe acute pain and the development of chronic pain. In such studies, it may be necessary to include interactions between biomedical and psychosocial risk factors [24,27], as well as temporal aspects of these risk factors, to fully account for the finding that individuals with more severe acute pain are more likely to develop chronic pain.

IMPLICATIONS FOR THE PREVENTION OF CHRONIC PAIN

The results of the studies of risk factors reviewed in this article have important implications for the prevention of chronic pain in individuals with acute pain. As Roberts suggested almost 15 years ago in discussing the treatment of chronic pain, "Perhaps the greatest single need at this time is to shift our focus to prevention rather than treatment. Prevention programs should be developed for patients at risk to develop chronic pain" [83]. But as Linton has recognized in discussing the development of such prevention programs, risk factors must first be identified before measures to eradicate them can be initiated [62].

The research reviewed in this article indicates that severe acute pain is a major risk factor for chronic pain. An important implication of this finding for the prevention of chronic pain is that acute pain should be minimized, both by reducing its intensity and by shortening its duration. For example, it has been suggested that the combination of antiviral therapy [8,91,104] and aggressive analgesic treatment [47] in patients with acute herpes zoster would be expected to reduce neural damage and acute pain and thereby lessen the risk of PHN [27]. In patients undergoing amputations, continuous epidural blockade for 72 hours before surgery reduced the incidence of phantom limb pain 6 months later [4], and continuous postoperative regional analgesia for 72 hours after amputation was followed by the complete absence of phantom pain in a sample of 11 patients up to 1 year later [32]. Katz and Melzack have suggested that the combined use of preoperative spinal analgesia and general anesthesia for amputations would be expected to reduce the incidence of phantom pain by blocking the somatosensory and cognitive memory systems that underlie the unified experience of pain [51,52,55].

In the model presented above, psychosocial factors are determinants of the affective/cognitive component of acute pain as well as risk factors for the development of chronic pain. Further reductions in the incidence of chronic pain might therefore be achieved by reducing the psychological distress that accompanies acute pain. There are a variety of techniques that

could be used to reduce distress associated with acute pain, including, for example, relaxation exercises, training in various coping strategies, patient education programs, and hypnosis. Based on the contribution of psychosocial risk factors to the development of chronic back pain, a number of studies have examined the efficacy of preventive interventions that emphasize psychosocial factors in patients with acute back pain [36,63,64,75]. In recent discussions of such interventions, it has been suggested that medical personnel should attend to the psychological characteristics of their acute back pain patients to prevent prolonged disability [40] and that preventive interventions should be "early, active, and oriented toward health behaviors" [63]. It is likely that these recommendations are applicable to all individuals with acute pain who have an increased risk of developing chronic pain, not just to those with acute back pain.

Many of the issues involved in the prevention of chronic pain in individuals with acute pain have been considered in discussions of preemptive analgesia and the reduction of postoperative pain. The literature reviewed in this article is certainly consistent with recent efforts to reduce postoperative pain by reducing perioperative pain [53,54,81,94,106] and psychosocial distress [52,101]. Only by means of controlled trials will it be possible to determine whether prolonged pain can be prevented by psychosocial interventions administered in combination with aggressive analgesia for acute pain and preemptive analgesia for surgery.

Acknowledgments *Supported by Grant NS-30714 from the National Institute of Neurological Disorders and Stroke and Grant MH-51791 from the National Institute of Mental Health. The author thanks Dr. Sharon Gordon and Dr. Malvin Janal for very helpful discussions of these issues.*

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Toward a Clearer Specification of Acute Pain Risk Factors and Chronic Pain Outcomes

Robert H. Dworkin

The goals of my Focus article were to call attention to the value of prospective studies of risk factors for chronic pain in individuals with acute pain and to review the results of the research that has been conducted to date. Although all three Commentaries agree that such studies are worthwhile, there is some disagreement regarding the extent to which the literature supports the conclusions of my review. Because an increasing number of prospective studies of the development of chronic pain are being conducted, it can be expected that the conclusions of my review will require updating before too long. Therefore, instead of discussing our differences on a point-by-point basis, I address an issue that was neglected in the Focus article but that was raised in each of the three Commentaries.

Based on a review of studies of phantom pain, chronic back pain, and postherpetic neuralgia, I concluded that severe acute pain is a major risk factor for the development of chronic pain. What was missing from this summary of the literature, however, was a discussion of the meaning of the terms *severe acute pain* and *chronic pain*. These risk factors and outcomes must be clearly specified, however, in designing future studies, in examining the mechanisms underlying relationships between acute pain and chronic pain, and in developing preventive interventions.

With respect to the identification of severe acute pain as a risk factor for chronic pain, studies that examined pain intensity were emphasized in the Focus article. It was suggested that future research should also evaluate the distinction between sensory and affective components of pain as well as specific pain qualities (e.g., burning, lancinating). Although measures of sensory and affective pain intensity and quality would be integral components of any comprehensive study of acute pain, other aspects of an individual's experience of acute pain should also be examined.

One very important consequence of pain is its impact on quality of life, and in future research it would be essential to assess the disability associated with acute pain. Disability is, itself, multidimensional, and the impact of acute pain on physical, social, and occupational functioning as well as on health care utilization should be evaluated. This would make it possible to determine whether it is greater acute pain intensity that places an individual at risk for chronic pain or whether it is the disability accompanying more intense acute pain that causes pain to become chronic.

As noted in the Commentaries, this question has important implications for understanding the mechanisms involved in the development of chronic pain. These mechanisms are likely to be different for different pain syndromes. When pain intensity is a major risk factor, then processes such as central sensitization and reorganization may play an important role in the development of chronic pain; however, when the disability associated with acute pain accounts for the development of chronic pain, then processes such as physical deconditioning may augment acute pain and prevent recovery. Identifying the mechanisms underlying risk factors for chronic pain has clear implications for developing preventive interventions. For example, if central sensitization underlies chronic pain, then aggressive analgesic interventions in acute pain patients may prevent chronic pain; however, as noted by Atkinson and his colleagues, if the disability associated with severe acute pain underlies the development of chronic pain, then reducing acute disability might be an effective preventive intervention.

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It is also important to evaluate the duration of acute pain when doing so would be meaningful, for example, the duration of preamputation pain. In conditions where pain is continuous, however, assessing the duration of acute pain would be problematic; this is because the distinction between acute and chronic pain is based on pain duration and all patients with chronic pain will, therefore, have had acute pain of maximum duration. Nevertheless, the manner in which acute pain and chronic pain are distinguished is a crucial feature of studies of the development of chronic pain. Different risk factors may be identified when different definitions of chronic pain are examined (e.g., pain lasting more than 6 months vs pain lasting more than 3 months from healing [5]). In addition, comparisons of risk factors—and of other clinical and pathophysiologic findings—using different definitions of acute and chronic pain have the potential to provide an empirical basis for determining when acute pain resolves and chronic pain begins.

It would also be possible to combine two or more of the above aspects of acute pain into summary measures that might better identify individuals with the greatest risk of developing chronic pain. For example, it has been suggested that a combined measure of pain intensity and duration be used in clinical trials in acute herpes zoster to reflect the total burden of pain experienced by the patient [1,6]. Likewise, it is possible that combined measures of pain intensity and disability, such as those examined in recent studies of back pain [2,3], may predict chronicity better than either measure alone.

A final aspect of the severity of acute pain is its treatment. Any comprehensive evaluation of acute pain severity as a risk factor for chronic pain should examine whether and how acute pain is treated. It is possible that the relationship between greater acute pain intensity and an increased risk for the development of chronic pain varies depending on treatment; for example, moderate acute pain in a patient receiving strong opioids may be associated with a greater risk of chronic pain than is moderate acute pain in an untreated patient.

The nature of the chronic pain outcomes examined in studies of acute pain and included in the model proposed in the Focus article must also be clearly specified. The outcome examined in a prospective study of acute pain is, of course, one of its central features, and different outcomes have been examined in different studies. In some studies, the simple presence of any pain at a given follow-up interval has been considered chronic pain (e.g., pain at 6 months after the onset of acute back pain [7]), whereas in other research, pain-related disability has been the outcome of interest (e.g., failure to return to work following an episode of acute back pain [2,3]).

It would not be at all surprising if different risk factors were ultimately identified for different chronic pain outcomes, specifically, for the later presence of any pain, however mild; for pain of moderate or greater intensity with minimal disability; and for pain accompanied by significant disability and/or psychosocial distress [8,9]. Indeed, prospective studies of acute pain will make it possible to determine whether patients who are coping well with relatively low levels of chronic pain (so-called "adaptive copers" [8]) have, over time, developed effective coping strategies for minimizing pain and disability or whether these are individuals who from the outset experienced minimal disability because their pain was never more than mild.

The selection of the specific chronic pain outcome to be examined in a prospective study of acute pain will depend, in part, on the primary goal of the research. As noted at the beginning of the Focus article, prospective studies of acute pain have important implications for understanding the pathogenesis of chronic pain, for designing preventive interventions, and for identifying those most in need of such interventions. If the primary goal of a prospective study is understanding the pathogenesis of prolonged pain, then any pain, regardless of its intensity and whether or not it is accompanied by disability, may be the outcome of greatest interest. If the primary goal, however, is to design preventive interventions and identify those most in need of such efforts, then outcomes characterized by greater personal suffering and social costs must be examined. This is because screening and prevention programs will be costly, especially with prevalent conditions such as acute back pain and herpes zoster. Of course, with a large sample and with enough measures administered at the baseline and follow-up assessments, it would be possible to compare risk factors for different chronic pain outcomes within a single study.

Almost 30 years ago, Mednick and McNeil published a now classic article entitled Current Methodology in Research on the Etiology of Schizophrenia: Serious Difficulties Which Suggest the Use of the High-risk Method [5]. They argued that identifying etiologic factors had been the goal of much schizophrenia research, but that studies of schizophrenic patients could not satisfactorily identify such factors because the characteristics of patients may be a consequence of their disorder or of its treatment. This observation provided the impetus for their proposal that future research on etiology and prevention should prospectively examine individuals at "high risk" for the later development of schizophrenia.

Current research on chronic pain is characterized by the very same "serious difficulties which suggest the use of the high-risk method" identified by Mednick and McNeil, that is, the difficulties associated with attempting to identify factors that contribute to the development of a disorder in patients who already

have the disorder. Prospective multivariate studies of individuals with acute pain, although requiring a major commitment of time and resources, are needed to address these difficulties. If our goal is to understand the pathogenesis of chronic pain, studies of chronic pain patients may contribute worthwhile information when conducted in tandem with these prospective studies. With respect to the prevention of chronic pain, however, research on patients who already have chronic pain is of limited value; it is only the results of prospective studies that will make it possible to design and evaluate preventive interventions that have the potential to eradicate chronic pain.

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Chapter 16

A Vulnerability–Diathesis–Stress Model of Chronic Pain: Herpes Zoster and the Development of Postherpetic Neuralgia

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SARA M. BANKS

> For that which is but a flea-biting to one, causeth insufferable torment to another; and which one by his singular moderation and well-imposed carriage can happily overcome, a second is no whit able to sustain. . . .
>
> —ROBERT BURTON, *The Anatomy of Melancholy*, 1621
> (cited in Kendler et al., 1995, p. 833)

The natural history, pathophysiology, and treatment of pain in herpes zoster ("shingles") and postherpetic neuralgia (PHN) have been reviewed in a number of publications (Dworkin & Johnson, 1998; Dworkin & Portenoy, 1996; Kost & Straus, 1996; Loeser, 1990; Portenoy, Duma, & Foley, 1986; Rowbotham, 1994; Watson, 1993; Watson & Evans, 1986), and we therefore do not review this material again in this chapter. Rather, our aim is to present a model of the pathogenesis of chronic pain in patients with herpes zoster. We begin by reviewing representative multifactorial models of the development of chronic pain and then compare these with diathesis-stress models of psychopathology. We then present a vulnerability-diathesis-stress model of chronic pain. Following the description of this model, we review studies of risk factors for chronic pain in herpes zoster patients. The results of these studies are then used as a basis for applying our model of the pathogenesis of chronic pain to the development of PHN.

MULTIFACTORIAL MODELS OF THE PATHOGENESIS OF CHRONIC PAIN

Despite the long-standing recognition that chronic pain develops from and is maintained by a combination of neurobiological, psychological, and social factors, surprisingly few comprehensive models have been proposed that explain the pathogenesis of chronic pain in terms of an interaction between biological and psychosocial factors. Those models that have done so remain at the conceptual and descriptive stages of model development and have yet to progress to the predictive stage. Although these

models have been comprehensive, including multiple factors and suggesting that there are interactive relationships among them, they have not specified how these factors interact nor have they proposed specific testable predictions about these factors and their relationships. We briefly describe three recent and representative biopsychosocial models of chronic pain to illustrate these limitations and the need for additional models of the pathogenesis of chronic pain.

S. F. Dworkin, Von Korff, and LeResche (1992) presented a comprehensive ecological model of chronic pain that synthesizes biopsychosocial components with three perspectives of epidemiology—the population perspective, the developmental perspective, and the ecological perspective. In keeping with the biopsychosocial perspective, these authors proposed an interaction between physiological factors that influence nociception, psychological factors that affect pain perception and appraisal, and social factors that shape pain behaviors and social roles. However, the model went beyond traditional biopsychosocial models in suggesting that the nature of the interactions between the biopsychosocial variables is dynamic rather than static—that these factors are in a dynamic flux and interact differently at different points in time. Consequently, the model introduced the construct of time and operationalized it along two dimensions: life span development and natural history of pain.

Kerns and colleagues (Kerns & Jacob, 1995; Kerns & Payne, 1996) presented a model for the development of persistent pain, disability, and distress in chronic pain patients. They proposed that an individual may have preexisting vulnerabilities in any one or a combination of cognitive, affective, behavioral, social, and biological domains that place that individual at risk for developing chronic pain following the experience of acute pain. In addition, they suggested that the experience of acute pain may create challenges or stressors for the individual across these same domains. Kerns and colleagues hypothesized that individuals in whom there is a match between a vulnerability and a specific challenge or stressor may go on to develop chronic pain and its associated disability and distress. In other words, the stressors associated with acute nociception were hypothesized to activate preexisting vulnerabilities to produce the clinical manifestations of the chronic pain syndrome. Akin to S. F. Dworkin et al.'s (1992) ecological model, the model proposed by Kerns and colleagues emphasized a temporal context in which biopsychosocial variables interact. It also emphasized the social and family context of the pain experience, within which interpersonal interactions exert change and maintenance effects on the chronic pain patient's functioning primarily by way of operant learning.

Flor and colleagues (Flor & Birbaumer, 1994; Flor, Birbaumer, & Turk, 1990; Turk & Flor, 1984) proposed a psychobiological model of chronic musculoskeletal pain that highlights the dynamic interaction among psychological and biomedical variables. Specifically, these authors suggested several interacting preconditions for the development and maintenance of chronic pain syndromes:

1. *Predisposing factors*—physiological predispositions that consist of a reduced threshold for nociceptive activation that may be related to genetic variables, previous trauma, or social learning experiences and that result in a physiological response stereotypy of a specific body system.
2. *Precipitating stimuli*—persistent aversive external or internal stimuli with negative meaning that activate the sympathetic nervous system and/or various muscular processes and also motivate avoidance responses.
3. *Precipitating responses*—maladaptive information processing of and coping with pain-related social and/or physiological stimuli.
4. *Maintaining processes*—operant, respondent, and observational learning processes that serve to maintain pain.

Similar to the model of Kerns and colleagues (Kerns & Jacob, 1995; Kerns & Payne, 1996), the model proposed by Flor and colleagues emphasized not only that premorbid vulnerabilities interact with stressors but also that learning processes contribute to the maintenance of chronic pain; both models were described by their authors as diathesis–stress models of chronic pain.

Each of these three models proposes that biological, psychological, and social factors are essential in understanding the pathogenesis of chronic pain. Two of the models even conceptualized the development of chronic pain in terms of preexisting vulnerabilities and stressors that combine in some way to produce the clinical manifestations of the chronic pain syndrome. However, none of the models specified which factors are necessary and which are sufficient for the emergence of chronic pain, and none included hypotheses about how the various factors may combine to produce chronic pain (e.g., whether in an additive fashion or through an interaction). Neither the descriptions of the models nor the illustrative figures that accompanied them offered specific predictions that could be subjected to statistical testing.

For example, S. F. Dworkin et al. (1992) suggested that "chronic pain and chronic pain behavior result from the dynamic interaction of nociception, pain perception, pain appraisal, behavioral response to pain, and social roles for persons in pain" (p. 4), but went no further in defining what is meant by dynamic interaction. The authors' suggestion that the biopsychosocial variables coexist in a dynamic flux over two dimensions of time may actually defy generation of testable hypotheses. In fact, the authors state that "the large number of possibilities for the interaction of these biologic, psychologic, and social factors through the different stages of development of pain dysfunction allows for highly varied individual expression of subjective pain experience and overt pain behaviors" (p. 5). Kerns and Jacob (1995) proposed "a congruence between a preexisting vulnerability to develop chronic pain and a specific challenge or stress represented by the pain problem" (p. 330), but again they did not describe precisely what is meant by congruence and whether this congruence must occur within the biological or psychosocial domains or between these domains of functioning. That is, there was little discussion of how or if the vulnerabilities and challenges within the psychosocial domains interact with the vulnerabilities and challenges within the biological domain. Finally, although Flor and colleagues (Flor & Birbaumer, 1994; Flor et al., 1990) described potential mechanisms for how predisposing factors, precipitating stimuli, precipitating responses, and maintaining processes may lead to chronic pain, their descriptions were again largely conceptual and lacked specific testable predictions.

These three models and much current theory and research on chronic pain are based, at least nominally, on a biopsychosocial approach in which the interaction of biological, psychological, and social factors is thought to account for the development of chronic pain (Turk, 1996). Surprisingly, however, in the recently published *Curriculum on Pain for Students in Psychology* (International Association for the Study of Pain, 1997), little attention is paid to the role of psychosocial factors in the etiology of chronic pain, and no mention at all appears of the interaction between biological and psychosocial factors. Perhaps this neglect is a result of the failure of most existing biopsychosocial models of chronic pain to provide an adequate basis for specifying testable hypotheses. In the next section, we briefly review major diathesis–stress models of psychopathology from the perspective of providing a framework for our model of the pathogenesis of chronic pain.

DIATHESIS–STRESS MODELS OF PSYCHOPATHOLOGY

Thirty years ago, Mednick and McNeil (1968) published a now classic article titled "Current methodology in research on the etiology of schizophrenia: Serious difficulties which suggest the use of the high-risk method." They argued that identifying etiological factors had been the goal of much schizophrenia research but that studies of individuals with schizophrenia could not satisfactorily identify such factors because the characteristics of patients may be a consequence either of their disorder or of its treatment. This observation provided the impetus for their proposal that future research on the etiology of schizophrenia could identify causal factors by examining individuals at "high risk" for the later development of the disorder using prospective methods.

This attention to distinguishing causal antecedents of a disorder from abnormalities that may be concomitants or consequences of the disorder remains an important focus of research on psychopathology (e.g., Haynes, 1992; Kraemer et al., 1997). One important result has been the development of diathesis–stress models in which it is hypothesized that psychopathology is caused by specific interactions between biological and psychosocial processes. These models of psychopathology have had enormous heuristic value and are central components of theory and research on diverse psychiatric disorders. Unfortunately, such attempts to specify the nature of the interactions between biological and psychosocial processes have not been characteristic of theory and research on the etiology of chronic pain. When compared to the biopsychosocial approaches discussed in the previous section, the most important advantage of diathesis–stress models of psychopathology is their greater emphasis on the investigation and identification of specific interactions between biological and psychosocial causal factors.

We believe such models are very valuable, not only in understanding psychopathology but also as a guide to future theory and research on the pathogenesis of chronic pain. In this section, we therefore briefly review several diathesis–stress models of the etiology of schizophrenia and depression that can provide a basis for a diathesis–stress model of the pathogenesis of chronic pain. In these models, an interaction between an organic predisposition (the diathesis) and psychosocial stress is hypothesized to account for the development of a disorder. The diathesis may be a genetic vulnerability, a disease,

an injury, or another predisposing condition of the organism. The psychosocial stress components of these models have included stressful life events, diminished social support, and various aspects of personality and psychopathology.

Current diathesis–stress models of psychopathology originated in theories of the etiology of schizophrenia (Meehl, 1962; Rosenthal, 1963). Two diathesis–stress models of schizophrenia that have had great influence are Zubin and Spring's (1977) vulnerability model and Nuechterlein and Dawson's (1984) vulnerability–stress model. Zubin and Spring proposed that vulnerability to schizophrenia is a relatively permanent, enduring trait and that "each of us is endowed with a degree of vulnerability that under suitable circumstances will express itself in an episode of schizophrenic illness" (p. 109). They suggested that there are numerous factors contributing to an individual's degree of vulnerability, including not only genetic influences but also acquired components of vulnerability resulting from, for example, perinatal complications, family experiences, and "other life events that either enhance or inhibit the development of subsequent disorder" (p. 109). The essence of Zubin and Spring's model was the proposition that an individual's vulnerability to schizophrenia determines how readily an episode of illness occurs in response to "challenges," which include endogenous biochemical or neurophysiological events as well as exogenous challenges, such as stressful life events. The hypothesized relationship between the degree of vulnerability and the degree of stress needed for illness to occur is illustrated in Figure 16.1. As can be seen from the figure, a highly vulnerable individual will cross the threshold into an episode of illness in response to a minimal challenge, whereas the individual with a low level of vulnerability requires a considerable degree of stress to become ill.

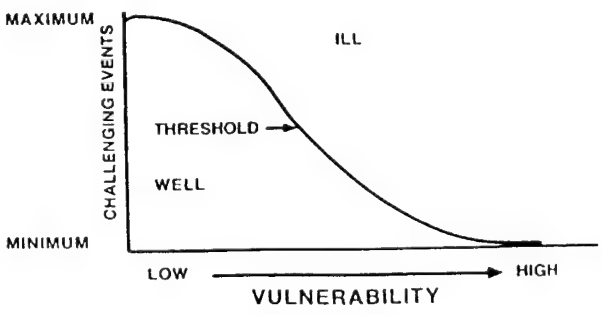

FIGURE 16.1. Relation between vulnerability and challenging events. From Zubin and Spring (1977). Copyright 1977 by the American Psychological Association. Reprinted by permission.

Nuechterlein and Dawson (1984) proposed a vulnerability–stress model of schizophrenia that was based on the results of longitudinal studies of psychological and psychophysiological abnormalities, stressful life experiences, and outcome in individuals with schizophrenia. Their model included both the vulnerability factors and the environmental challenges that had been discussed by Zubin and Spring (1977). In addition, the model identified specific sets of vulnerability factors and environmental factors that were hypothesized to interact with each other. Importantly, Nuechterlein and Dawson's model also included feedback loops between these factors and transient intermediate states that might or might not progress to a full episode of illness.

The transient intermediate states in this model provide a point at which the vicious cycle between vulnerability and stress and progressively increasing dysfunction can be interrupted. This attention to the possibility of prevention was one of the most important contributions of Nuechterlein and Dawson's (1984) model. Before prevention can be attempted, it is first necessary to identify those individuals who require preventive efforts and to specify the point at which prevention becomes needed. Nuechterlein and Dawson distinguished stable vulnerability indicators, mediating vulnerability factors, and episode indicators. Stable vulnerability indicators are present before, during, and after episodes of illness and, as can be seen from the top panel of Figure 16.2, are independent of changes in symptoms. Nuechterlein and Dawson noted that stable vulnerability indicators could be used to identify individuals at risk for the development of schizophrenia but that their accuracy will be incomplete because the indicators may be present in individuals who never develop the disorder. Mediating vulnerability factors are also deviant during the disorder and when the individual is asymptomatic, but they differ from stable vulnerability indicators because they covary with symptomatology, as the middle panel of Figure 16.2 shows. Mediating vulnerability factors were hypothesized to play a role in the causal chain of events leading to schizophrenia and to become more deviant during the transient intermediate states preceding an episode of the disorder. Changes in mediating vulnerability factors therefore have the potential to predict an impending episode of disorder. Nuechterlein and Dawson distinguished these two types of

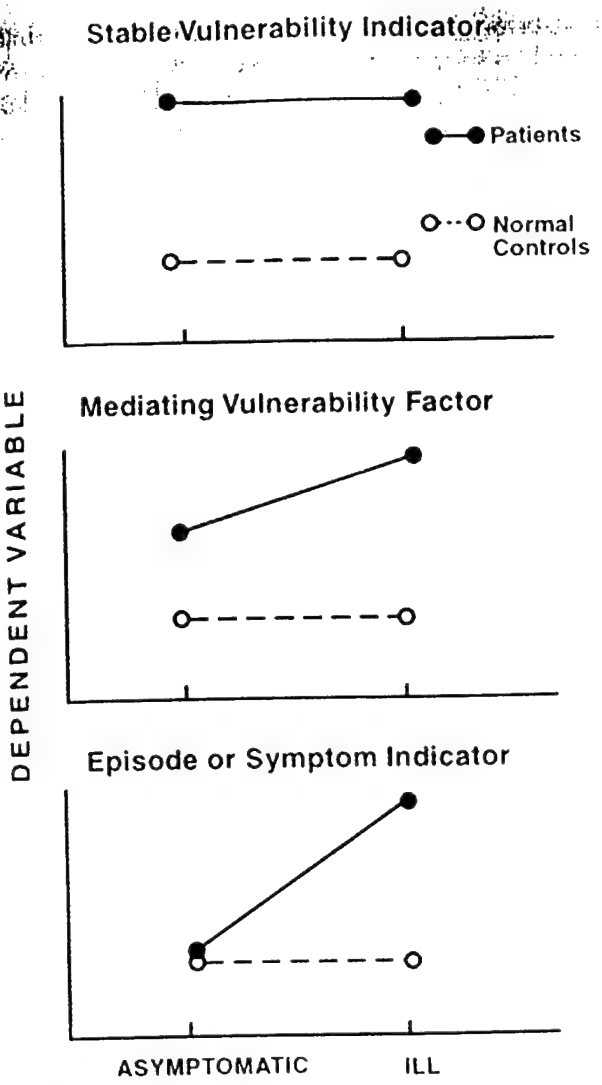

FIGURE 16.2. Characteristic patterns across clinical states for stable vulnerability indicators, mediating vulnerability factors, and episode or symptom indicators. Adapted from Nuechterlein and Dawson (1984).

vulnerability factors from episode or symptom indicators. As can be seen from the bottom panel of Figure 16.2, episode indicators are normal when the individual is asymptomatic—that is, before and after episodes of illness—but are deviant when the individual is ill. Such indicators have little value in distinguishing causal antecedents from consequences of a disorder and no value in predicting onset, but they can be used to evaluate clinical improvement and treatment efficacy (see Kraemer, Gullion, Rush, Frank, & Kupfer, 1994, for another approach to distinguishing the state and trait components of measures used in psychopathology research).

These two models of schizophrenia have been very influential and continue to be revised and refined (e.g., Green, 1998; Nuechterlein et al., 1992). Similar diathesis–stress models of depression have also been proposed. In an important series of studies, Kendler and colleagues have presented and tested an "integrated etiologic model" of depression (Kendler, Kessler, Neale, Heath, & Eaves, 1993, p. 139; Kendler et al., 1995). This model proposes that at least four major interacting risk factor domains play a role in the etiology of major depression—genetic factors, traumatic experiences, temperament, and interpersonal relations. The model includes the vulnerability factors (e.g., genetic factors, parental loss) and stressful life events that have been the central components of diathesis–stress models of schizophrenia. The results of a recent study provided evidence of a statistically significant interaction between genetic vulnerability and stress in which the increased risk of depression following a stressful life event was significantly greater for individuals with high levels of genetic vulnerability than for those with lower levels of genetic vulnerability (Kendler et al., 1995).

As researchers in schizophrenia and depression have recognized, interactions between diathesis (or vulnerability) and stress may take many forms (e.g., Kendler & Eaves, 1986; Monroe & Simons, 1991). For some disorders, the diathesis may not interact at all with stress, and the development of illness may be a result of additive effects of these factors, as illustrated in the top panel of Figure 16.3. For other disorders, diathesis and stress may interact. For example, stress may have a greater effect in individuals with a more severe diathesis than in individuals with little or no vulnerability, the interaction found by Kendler et al. (1995) and shown in the middle panel of Figure 16.3. It is also possible that stress may have a greater effect in individuals with a moderate diathesis than in those whose diathesis is either high or low in severity, as the bottom panel of Figure 16.3 shows. Other models of the interaction between diathesis and stress are possible, including those with threshold effects for either the diathesis or stress components of the model and those in which diathesis and stress are not independent (e.g., the diathesis may influence the individual's exposure to stress; Kendler & Eaves, 1986; Monroe & Simons, 1991). It is this emphasis on specifying testable hypotheses about interactions between risk factors that we believe is the most valuable feature of diathesis–stress models of psychopathology. Indeed, the strength of these models is in their "in-depth probing of associations between the components of the model, often multidirectional and transpiring over time" (Monroe & Simons, 1991, p. 422).

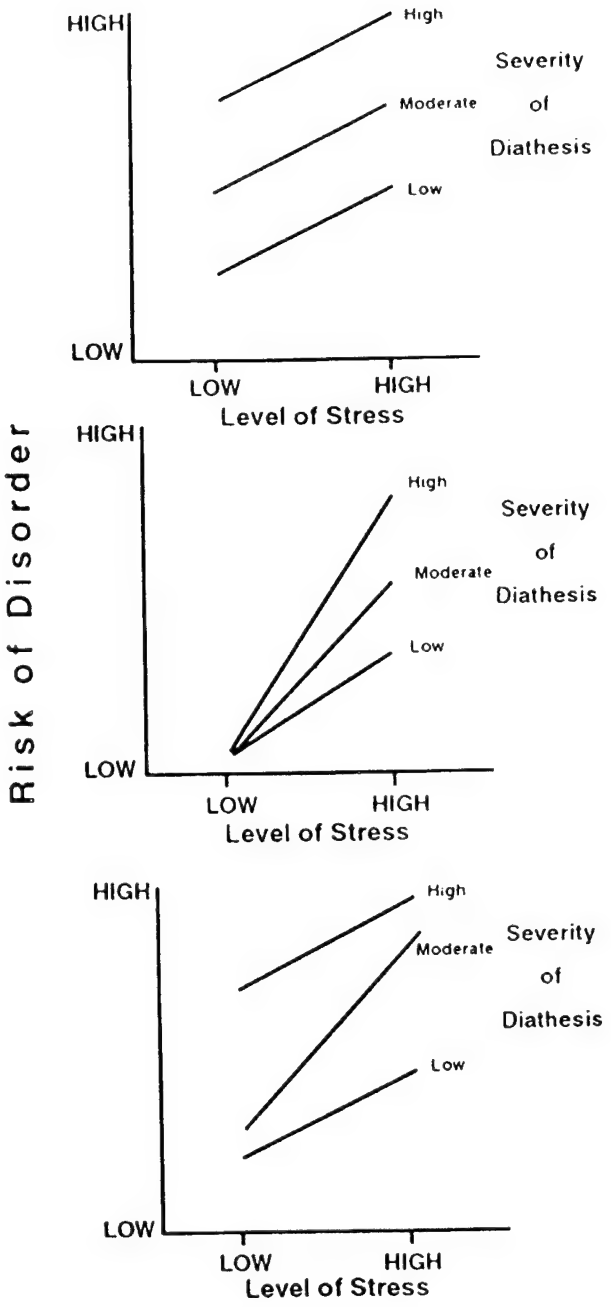

FIGURE 16.3. Hypothetical relationships between diathesis and stress.

A VULNERABILITY-DIATHESIS-STRESS MODEL OF CHRONIC PAIN

In this section, we propose a vulnerability-diathesis-stress model of the pathogenesis of chronic pain that not only includes biological, psychological, and social factors but that also makes it possible to examine hypothesized interactions among these causal factors. In this model, the pathogenesis of chronic pain originates in neurobiological and psychosocial predisposing factors that precede the onset of pain. The neurobiological factors that predispose individuals to develop chronic pain are undoubtedly diverse. They include the genetic factors that underlie individual differences in physiology or structure that make an individual more likely to develop chronic pain (e.g., sympathetic reactivity, scoliosis). These neurobiological factors also include physiological and structural abnormalities resulting from prior disease or injury or their treatment (e.g., diabetic neuropathy, musculoskeletal pathology). Although it is beyond the scope of this chapter to review these neurobiological predisposing factors, few prospective studies have been conducted that directly address such factors in the development of chronic pain. Accordingly, much of our very limited understanding of neurobiological predispositions for chronic pain is indirect and consists of informed hypotheses that are based on animal models, clinical observations, and studies of patients already suffering from chronic pain.

The psychosocial factors that predispose individuals to develop chronic pain are also likely to be diverse. Such factors probably include pain-relevant personality traits (e.g., somatization, somatic amplification, hypervigilance; Dworkin, 1997a; Gamsa, 1994a, 1994b; McDermid, Rollman, & McCain, 1996) and psychopathology, perhaps especially mood, anxiety, and substance abuse disorders (e.g., Atkinson, Slater, Patterson, Grant, & Garfin, 1991; Banks & Kerns, 1996; Dworkin, 1997a; Dworkin & Gitlin, 1991; Walker, Keegan, Gardner, Sullivan, Katon, et al., 1997). Physical and sexual abuse and other traumatic events (e.g., emotional abuse and neglect) occurring before the onset of pain, perhaps especially during childhood, also appear to be risk factors for the development of chronic pain (e.g., Linton, 1997; Schofferman, Anderson, Hines, Smith, & Keane, 1993; Schofferman, Anderson, Hines, Smith, & White, 1992; Walker, Keegan, Gardner, Sullivan, Bernstein, et al., 1997). In addition, the individual's prior experiences with pain may also be a psychosocial predisposing (or protective) factor (Bachiocco, Scesi, Morselli, & Carli, 1993; Dar, Ariely, & Frenk, 1995), although it is also possible that such experiences result in, for example, central sensitization or increased descending inhibition and could therefore be considered neurobiological predisposing factors. Other pain-relevant attitudes, beliefs, and behaviors that are a consequence of the individual's socialization experiences and that develop during childhood and adolescence are very likely to be psychosocial predisposing factors (e.g., Grunau, Whitfield, Petrie, & Fryer, 1994). For example, modeling of responses

to pain and illness by significant others in childhood and adolescence is commonly thought to be an important influence on how an adult responds to a painful injury or illness (e.g., Chaturvedi, 1987; Violon & Giurgea, 1984). Unfortunately, however, virtually all existing studies of this question make it impossible to distinguish the relative effects of shared genetic and environmental influences (but see the adoption study of somatoform disorders conducted by Bohman, Cloninger, von Knorring, & Sigvardsson, 1984).

In our proposed vulnerability–diathesis–stress model of chronic pain, the neurobiological and psychosocial predisposing factors that precede the onset of pain constitute the vulnerability component of the model. This vulnerability is conceptualized as a continuum to which both the neurobiological and psychosocial predisposing factors contribute. Individuals therefore range from low to high in their vulnerability to the development of chronic pain. The neurobiological and psychosocial predisposing factors may contribute to this continuum of vulnerability in an additive fashion, or interactions within and between these two domains of risk factors may occur.

D. Cohen (1974) proposed that the etiology of neurosis is based on two sequential interactions—the first between organismic factors and socialization, which results in the individual having a "disposition" to develop a neurosis, and the second between this disposition and the environmental "condition," which results in the neurosis. As in Cohen's model and the vulnerability models of schizophrenia discussed previously, we propose that the individual's combined neurobiological and psychosocial predisposing factors constitute an enduring vulnerability to chronic pain that interacts with subsequent events. Our model differs from these, however, in proposing that this second interaction occurs between the individual's vulnerability and *two* other antecedents of chronic pain, a diathesis and stress. In our model, the diathesis for chronic pain is not the premorbid neurobiological and psychosocial vulnerability but rather is an illness or injury that causes an episode of acute pain. Because the distinction between acute and chronic pain is based on pain duration (e.g., 3 months; Merskey & Bogduk, 1994), all chronic pain patients, by definition, have suffered from acute pain that did not resolve. The presence of acute pain, therefore, places a person at risk for the subsequent development of chronic pain.

We have therefore proposed that an illness or injury that causes an episode of acute pain is a necessary but not sufficient diathesis for the development of chronic pain (Dworkin, 1991; R. H. Dworkin et al., 1992; Dworkin & Portenoy, 1996). There are many examples of such diatheses: the diathesis for chronic low back pain is an acute back injury; the diathesis for reflex sympathetic dystrophy (complex regional pain syndrome, Type I) is trauma from a surgical procedure or a typically mild injury; the diathesis for phantom limb pain is amputation; and the diathesis for postherpetic neuralgia is acute herpes zoster. Although these diatheses are either present or absent in an individual, when present the diathesis should be considered a continuum of severity. Individuals therefore vary from low to high with respect to how severe their diathesis is, that is, the degree to which their diathesis places them at risk for the development of chronic pain. For most diatheses, this continuum of severity is probably reflected in the severity of the acute pain that accompanies the diathesis. This acute pain, at least in part, reflects the pathophysiological process or processes that not only contribute to acute pain but also increase an individual's risk for the development of chronic pain (Dworkin, 1997a). Strictly speaking, it is these pathophysiological processes that are the diatheses for chronic pain; unfortunately, however, current knowledge of the pathophysiology of chronic pain is limited, and our ability to directly measure the severity of the damage or dysfunction underlying acute and chronic pain is minimal.

As in the diathesis–stress models of psychopathology discussed above, we hypothesize that the diathesis for chronic pain interacts with the degree of psychosocial stress being experienced by the individual during the months directly preceding the injury or illness. A valuable guide to choosing the types of variables to be examined in this domain has been provided by the Dohrenwends and their colleagues (B. S. Dohrenwend & Dohrenwend, 1981; B. P. Dohrenwend, Shrout, Link, Martin, & Skodol, 1986), who propose that the "life-stress process" includes recent stressful life events and the relative absence of ongoing social supports. They suggest that these variables can be antecedents of both physical and psychological disorder—a hypothesis clearly applicable to chronic pain, a disorder which almost always involves both physical and psychological processes.

Relationships between stressful life events and the onset and course of physical illness have been reported frequently, and a number of studies have examined the relationship between stressful life events and various chronic pain syndromes (e.g.,

Affleck, Tennen, Urrows, & Higgins, 1994; Arena, Sherman, Bruno, & Smith, 1990; De Benedittis, Lorenzetti, & Pieri, 1990; Feuerstein, Sult, & Houle, 1985; Gervais et al., 1991; Marbach, Lennon, & Dohrenwend, 1988). Numerous associations between social support and susceptibility to and recovery from physical illness have also been found (S. Cohen, 1988; S. Cohen & Williamson, 1991), and the relationship between social support and chronic pain has been examined in several studies. The results of this research suggest that social support may have detrimental as well as beneficial effects in chronic pain patients (e.g., Gervais et al., 1991; Gil, Keefe, Crisson, & Van Dalfsen, 1987; Kerns, Haythornthwaite, Southwick, & Giller, 1990; Kerns, Southwick, Giller, Haythornthwaite, & Rosenberg, 1991; Kerns & Turk, 1984; Klapow et al., 1995; Marbach et al., 1988; Paulsen & Altmaier, 1995; Turk, Kerns, & Rosenberg, 1992).

There are complex conceptual and methodological issues involved in examining the relationships between social support and stressful life events and the development of a disorder such as chronic pain. Among these are the different models of the relationship between social support and health (e.g., direct effect vs. buffering models; S. Cohen, 1988) and the confounding of social support with preexisting psychological or physical disorder (e.g., psychologically distressed or physically disabled individuals may be less able to establish supportive relationships; Monroe & Steiner, 1986). There are a variety of methods that have been used to measure social support, and numerous distinctions have been made regarding different types, sources, and dimensions of social support (e.g., Dunkel-Schetter & Bennett, 1990; House, Umberson, & Landis, 1988; Smith, Fernengel, Holcroft, Gerald, & Marien, 1994; Wethington & Kessler, 1986).

Not surprisingly, a variety of different models of the relationship between life events and physical illness has also been proposed (S. Cohen & Williamson, 1991), and various suggestions have been made regarding the types of life events that have the greatest impact on health (e.g., Shrout et al., 1989). It has been recognized that the methods used to assess stressful life events have often led to a confounding with the consequences of physical and psychological disorder (e.g., marital difficulties can be a stressful event but they may also reflect psychopathology; B. S. Dohrenwend, Dohrenwend, Dodson, & Shrout, 1984; Schroeder & Costa, 1984); this problem, however, can be addressed by examining separately those life events that do not reflect such consequences. It has also been noted that although most existing measures of life events have focused on temporally discrete events, many physical and psychological disorders may be more closely associated with ongoing chronic stressors (e.g., Monroe & Roberts, 1990; Moos, 1992).

Many life events involve important changes in an individual's relationships, and so stressful life events often involve decreases in an individual's level of social support (Thoits, 1982). Indeed, Moos (1992) has argued that life events and social supports are closely interrelated and tend to influence each other over time and that an integrated approach to their assessment is therefore necessary. It is for this reason that the stress component of our vulnerability–diathesis–stress model of chronic pain comprises both stressful life events and the relative absence of social support (and any detrimental effects of its presence). We propose that this psychosocial stress interacts with the diathesis for chronic pain and that the relationships between diathesis and stress and the development of chronic pain vary depending on the individual's level of vulnerability.

An illustration of our model of the relationships between the individual's vulnerability, diathesis, and psychosocial stress and his or her probability of developing chronic pain is presented in Figure 16.4. As can be seen from the figure, individuals with low levels of neurobiological and psychosocial vulnerability have an overall lower risk of chronic pain than those with greater vulnerability (for clarity, we have chosen to represent vulnerability in this figure as dichotomous even though we believe, as discussed previously, that it is a continuum). Within these levels of vulnerability, diathesis and stress interact, with psychosocial stress having a more pronounced impact when the individual's diathesis is severe (of course, it is also possible that the diathesis and stress interact in a manner different from that depicted here, as illustrated in Figure 16.3). In this model, individuals with low levels of psychosocial and neurobiological vulnerability, little psychosocial stress at the time of their illness or injury, and a diathesis that is minimal in severity are not likely to develop chronic pain. However, those with high vulnerability, considerable stress, and a severe diathesis are at great risk of chronic pain. It is important to note that in this model low levels of vulnerability and stress can be thought of as serving to protect the individual from the development of chronic pain even when the diathesis is severe and that such effects

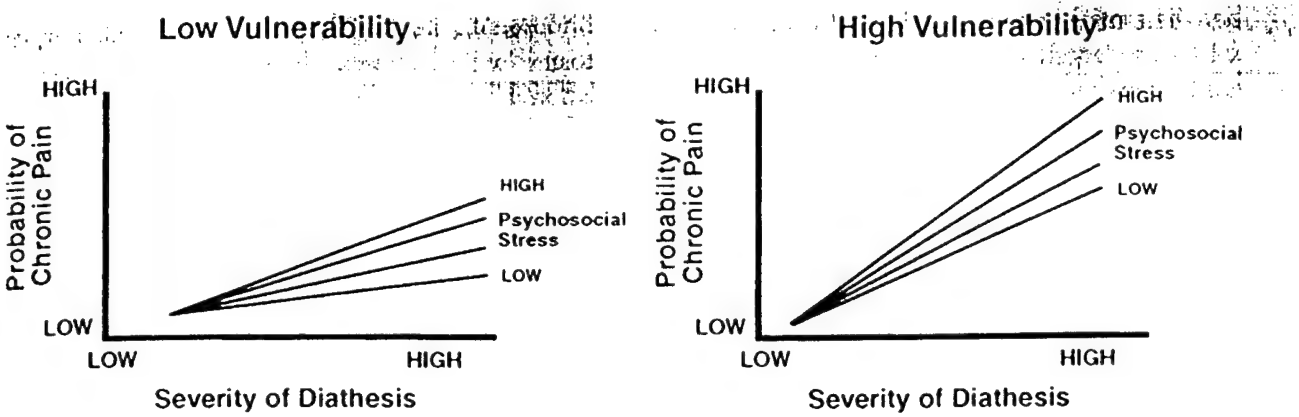

FIGURE 16.4. A vulnerability-diathesis-stress model of the pathogenesis of chronic pain.

have implications for the prevention of chronic pain (Dworkin, 1997a).

To this point, we have discussed chronic pain as something that is either present or absent. However, the nature of the chronic pain outcomes examined in the vulnerability-diathesis-stress model must be clearly specified. The outcome explained in a model of the pathogenesis of chronic pain is, of course, its central feature, and it would not be at all surprising if different risk factors were ultimately identified for different chronic pain outcomes (Dworkin, 1997b). Chronic pain has been defined differently in different studies, with 3 months and 6 months being the minimum durations most often used to identify samples of chronic pain patients. It has also been suggested that a combined measure of pain intensity and duration be used; this measure provides a continuous measure of chronic pain severity and reflects the total "burden" of pain experienced by the patient (Dworkin, Carrington, et al., 1997; Lydick, Epstein, Himmelberger, & White, 1995; Oxman et al., 1994).

But duration and intensity of pain are not the only variables that must be considered in defining chronic pain outcomes. Distinctions can be made between the presence of any pain, however mild; pain of moderate or greater intensity with minimal disability; and pain accompanied by significant disability and psychosocial distress (e.g., Klapow et al., 1993; Turk & Rudy, 1992; Von Korff, Ormel, Keefe, & Dworkin, 1992). Indeed, prospective studies designed to test the vulnerability-diathesis-stress model would make it possible to determine whether patients who are coping well with relatively low levels of chronic pain (so-called adaptive copers; Turk & Rudy, 1992) have, over time, developed effective coping strategies for minimizing pain and disability or whether these are individuals who from the outset experienced minimal disability because their pain was never more than mild.

The selection of the specific chronic pain outcome to be examined in testing the vulnerability-diathesis-stress model of chronic pain will depend, in part, on the primary goal of the research program. If this goal is understanding the pathogenesis of chronic pain, then any pain—regardless of its intensity and whether or not it is accompanied by disability—may be the outcome of greatest interest. If the primary goal, however, is to design preventive interventions and identify those most in need of such efforts, then outcomes characterized by greater personal suffering and social costs must be examined. This is because screening and prevention programs are costly, especially with prevalent conditions such as acute back pain. Of course, with a large sample and with enough measures administered at baseline and follow-up assessments, it would be possible to examine different chronic pain outcomes within a single study.

The vulnerability-diathesis-stress model is a model of the pathogenesis of chronic pain. Many of the factors included in the model may also be relevant to the maintenance of chronic pain once it is established and may contribute to an explanation of why, for example, chronic pain resolves considerably more quickly in some individuals than in others. Diverse factors have been implicated in the maintenance of chronic pain (e.g., Banks & Kerns, 1996; Feuerstein, Papciak, & Hoon, 1987; Gatchel, 1996; Rohling, Binder, & Langhinrichsen-Rohling, 1995; Waddell, Newton, Henderson, Somerville, & Main 1993), and such maintaining factors would need to be included in any comprehensive model intended to address the duration of chronic pain as well as its origins

The mechanisms by which chronic pain develops are largely unknown, and it is almost certainly true that these mechanisms are at least partially different for different pain syndromes. Our aim in proposing a vulnerability–diathesis–stress model of chronic pain is to provide a general framework for future research on the pathogenesis of chronic pain. It has been argued that research on psychosocial aspects of physical and psychological disorders has been hindered by a neglect of the possibility that the influence of psychosocial factors may be syndrome-specific (S. Cohen, 1988; S. Cohen & Williamson, 1991). If future prospective studies succeed in identifying antecedents of chronic pain and in distinguishing them from its concomitants and consequences, it will become possible to examine the applicability of our model to the wide variety of chronic pain syndromes that have been described (Merskey & Bogduk, 1994). Indeed, the results of recent studies suggest that our vulnerability–diathesis–stress model of chronic pain may also be applicable to acute pain (e.g., Bélanger, Melzack, & Lauzon, 1989; Syrjala & Chapko, 1995).

HERPES ZOSTER AND POSTHERPETIC NEURALGIA

The varicella-zoster virus (VZV) causes two different diseases: varicella (chicken pox), which typically occurs in children, and herpes zoster, which typically occurs in elderly individuals (Hope-Simpson, 1954; Weller, Witton, & Bell, 1958). The virus establishes latency in sensory ganglia following the varicella infection, and herpes zoster is the reactivation of the virus and its spread from a sensory ganglion to the corresponding dermatome (Hope-Simpson, 1965; Straus et al., 1984). Although the presentation of herpes zoster is variable, a prodrome of dermatomal pain typically precedes the appearance of the rash, which becomes pustular after several days and then forms a crust; thoracic dermatomes are the most commonly affected sites (Hope-Simpson, 1965; Portenoy et al., 1986). The nature and duration of pain in herpes zoster varies greatly among patients, and in a percentage of cases pain in the affected dermatome persists following the acute infection and healing of the rash (Dworkin & Johnson, 1998; Dworkin & Portenoy, 1996). Persisting herpes zoster pain is termed postherpetic neuralgia (PHN), a chronic pain syndrome that can last for years and cause substantial suffering.

As Weller (1992, p. S4) has noted, herpes zoster "will increase as the mean age of our population increases, reflecting both the age-related decay of cellular immunity and the enhanced propensity for malignancy in the elderly." PHN can therefore be expected to increase substantially in the next several decades (Donohue, Choo, Manson, & Platt, 1995; Schmader, 1995), not only because more individuals will develop herpes zoster but also because these elderly individuals will have an increased risk of PHN, as discussed subsequently. Unfortunately, even though numerous approaches are available for the treatment of PHN (Dworkin & Johnson, 1998; Watson, 1993), many patients either fail to respond or derive only limited benefit. Because PHN patients suffer from increased health care utilization, psychological distress, and physical and occupational disability (Davies, Cossins, Bowsher, & Drummond, 1994; Graff-Radford, Kames, & Naliboff, 1986), a substantial increase in the prevalence of PHN would be a major public health concern.

A greater understanding of the pathogenesis of PHN has the potential to contribute to the development of improved treatments and methods for reducing or even eliminating the risk that patients with acute herpes zoster will develop PHN. In the next section, we will review the results of research on risk factors for chronic pain in herpes zoster patients. The identification of individuals with acute herpes zoster who are at increased risk for the development of chronic pain has the potential to guide research on the pathogenesis of PHN. As we will discuss, the results of these studies provide support for a vulnerability–diathesis–stress model of PHN. In addition, knowledge of risk factors could be used in the design of interventions to prevent the development of PHN and to identify those individuals who most need such preventive efforts because of their increased risk of chronic pain (Dworkin, 1997a; see also Kraemer et al., 1997).

RISK FACTORS FOR CHRONIC PAIN IN HERPES ZOSTER PATIENTS

An increasing number of studies are being conducted in which the characteristics of acute herpes zoster patients who develop prolonged herpes zoster pain are being examined. The impetus for these studies has come from two sources. One is the examination of covariates in clinical trials that evaluate the impact of antiviral agents and other drugs on the persistence of pain in herpes zoster patients

(Dworkin, Carrington, et al., 1997). The second is research that seeks to increase understanding of the natural history and pathogenesis of PHN. Before reviewing these studies, we will discuss the different approaches that have been used to assess prolonged pain in herpes zoster—that is, to define the specific outcome for which some patients have an increased risk.

Assessing Prolonged Pain in Herpes Zoster

As discussed elsewhere (Dworkin, 1997c; Dworkin, Carrington, et al., 1997; Dworkin & Portenoy, 1996), a variety of approaches has been used to define PHN and to examine prolonged pain in herpes zoster patients. PHN has been defined as pain persisting after the herpes zoster rash has healed and as pain persisting beyond a specified interval after rash onset or after rash healing; for example, 3 months. The number of patients with persisting herpes zoster pain declines with time, and estimates of the prevalence of PHN—which range from 9% to 34%—vary with the criteria used to define it.

Because of the existence of different definitions of PHN, the use of a diagnosis of PHN in research on herpes zoster pain has recently become controversial. It has been suggested that pain in herpes zoster be considered "as a continuum, rather than distinguishing acute pain from an arbitrary definition of postherpetic neuralgia" (Huff et al., 1993, p. 93). Several recent studies have used this approach to examine the efficacy of various medications in reducing the duration of herpes zoster pain (e.g., Beutner, Friedman, Forszpaniak, Andersen, & Wood, 1995; Degreef, 1994; Whitley et al., 1996; Wood, Kay, Dworkin, Soong, & Whitley, 1996). In these trials, the primary endpoint used in evaluating treatment efficacy is the time from enrollment in the trial to complete cessation of all zoster-associated pain; no distinction is made between acute pain and PHN when herpes zoster pain is examined in this manner (Wood, 1995).

Such analyses of herpes zoster pain considered as a continuum can provide a worthwhile overview of factors associated with pain duration, not only in studies of the efficacy of treatments for reducing pain duration but also in research on risk factors for prolonged herpes zoster pain. One important advantage of examining herpes zoster pain as a continuum is that no assumption is required regarding the point at which PHN begins. However, to the extent that acute herpes zoster pain and PHN differ clinically and have different pathophysiologies, examining pain only as a continuum would be misleading and could impede progress in understanding herpes zoster.

The available data provide considerable support for the validity and importance of examining acute herpes zoster pain and PHN separately (Dworkin, 1997c; Dworkin, Carrington, et al., 1997; Dworkin & Portenoy, 1996). However, the two different approaches to the persistence of pain in herpes zoster are not mutually exclusive; data on herpes zoster pain collected on multiple occasions beginning during the acute infection and continuing for several months thereafter can be examined by using a continuum of pain duration as well as by analyzing the incidence and duration of PHN. Accordingly, in the following discussion of risk factors for chronic pain in patients with herpes zoster, findings based on a diagnosis of PHN, however defined, will be considered together with findings based on analyses in which herpes zoster pain is examined as a continuum of overall pain duration.

Greater Age

Until recently, the only factor that had been associated consistently with an increased risk of PHN was age (Brown, 1976; Burgoon, Burgoon, & Baldridge, 1957; Choo et al., 1997; De Moragas & Kierland, 1957; Guess, Broughton, Melton, & Kurland, 1985; Harding, Lipton, & Wells, 1987; Hope-Simpson, 1975; Raggozzino, Melton, Kurland, Chu, & Perry, 1982; Rogers & Tindall, 1971). PHN is infrequent in patients under 40, but as many as 65% of patients over 60 and 75% of those over 70 have pain at 1 month following healing; the proportion of patients with pain at 1 year approaches 50% in those over 70 (De Moragas & Kierland, 1957).

Greater Acute Pain Severity

The possibility that "there may be a correlation between the duration of pain and the severity of pain on presentation" in herpes zoster was proposed only several years ago as a hypothesis in need of further investigation (Wood et al., 1994, p. 900). However, there are now a considerable number of independent studies that have reported that patients with more severe acute pain are at greater risk for

both prolonged herpes zoster pain (assessed as a continuum) and for PHN (Bamford & Boundy, 1968; Beutner et al., 1995; Bruxelle, 1995; Dworkin, Boon, Griffin, & Phung, 1998; Dworkin, Cooper, Walther, & Sweeney, 1997; R. H. Dworkin et al., 1992; Fiddian, 1995; Haanpää & Nurmikko, 1997; Harding et al., 1987; Leijon, Boivie, Roberg, & Forsberg, 1993; McKendrick, Care, Ogan, & Wood, 1994; Molin, 1969; Riopelle, Naraghi, & Grush, 1984; Whitley et al., 1996; Wood et al., 1996). In addition, acute pain severe enough to interfere with activities of daily living has also been reported to be a risk factor for PHN (Choo et al., 1997; Galil, Choo, Donahue, & Platt, 1997). The majority of these studies examined the persistence of pain using a 6-month follow-up period; however, greater acute pain severity has also been reported to predict greater duration of pain in patients with pain resolving before rash healing (Bamford & Boundy, 1968), as well as presence of PHN 9 years after an acute herpes zoster infection (McKendrick et al., 1994).

A variety of research designs, pain measures, and approaches to examining prolonged pain have been used in these studies, and several have serious methodological shortcomings, including small sample sizes and the use of retrospective methods. Nevertheless, given that a relationship between greater acute pain severity and prolonged herpes zoster pain has been found in all of these studies, this relationship can now be considered an established finding. The focus of future research should therefore become the identification of mechanisms accounting for this relationship. In pursuing this task, a priority should be to conduct a careful examination of the specific aspects of acute herpes zoster pain that predict the development of chronic pain (Dworkin, 1997a, 1997b).

Few of the studies that have reported a relationship between the severity of acute herpes zoster pain and PHN have examined the different types of pain associated with herpes zoster. For example, is the predominant quality of patients' acute herpes zoster pain—whether allodynia, burning, throbbing, or stabbing (Dworkin & Portenoy, 1996)—associated with their risk of developing PHN? Burning pain is more common in PHN patients than in acute herpes zoster patients, who are more likely to report sharp, stabbing pain (Bhala, Ramamoorthy, Bowsher, & Yelnoorker, 1988; Bowsher, 1993). In addition, burning pain was much *less* likely to be reported by PHN patients who had been treated with acyclovir during their acute infection compared to PHN patients who had not received acyclovir (Bowsher, 1992, 1993). Acyclovir is an antiviral agent that inhibits VZV replication and may thereby limit the neural damage contributing to the development of PHN. Considered together, the greater prevalence of burning pain in PHN compared to acute herpes zoster and the reduced burning pain in PHN patients treated with acyclovir suggest that burning pain may reflect an important pathophysiological mechanism in the development of prolonged herpes zoster pain. It could therefore be hypothesized that acute herpes zoster patients with prominent burning pain are at greater risk for the development of PHN (Dworkin, 1997a). Preliminary reports of the results of two recent studies, however, suggested that patients who described their acute herpes zoster pain as sharp (Johnson, Shukla, & Fletcher, 1995) and who had mechanical allodynia (Haanpää & Nurmikko, 1997) were more likely to have pain that persisted 3 months after rash onset. Additional prospective studies are therefore needed to resolve the relationship between pain quality in herpes zoster and the development of PHN.

Greater Rash Severity

Several studies have reported that greater severity of the cutaneous manifestation of the acute herpes zoster infection is associated with prolonged herpes zoster pain and the development of PHN (Choo et al., 1997; Dworkin et al., 1998; Higa, Dan, Manabe, & Noda, 1988; Higa, Noda, Manabe, Sato, & Dan, 1992; Higa et al., 1997; Whitley et al., 1996; Wildenhoff et al., 1981; Wildenhoff, Ipsen, Esmann, Ingemann-Jensen, & Poulsen, 1979; Wilson, 1986). Rash severity has been assessed using a variety of methods in these studies. The duration of time until the occurrence of various aspects of rash healing has been examined, including assessments of time to cessation of new vesicle formation and time to complete crusting. In addition, assessments of rash severity have been conducted, including counts of the number of vesicles and ratings of the proportion of the dermatome affected. Few studies, however, have reported assessments of rash severity on multiple occasions, which would allow rash progression from onset to healing to be examined. Even fewer studies have evaluated the interrater reliability of their ratings of rash severity, ratings which often involve judgments with a subjective component.

Although scarring in the affected dermatome is common in patients following healing of the

acute herpes zoster rash, there are no studies that have examined the relationship between the severity of the acute zoster rash and the development of scarring. Two studies, however, have examined the relationship between scarring and PHN; it has been reported that the presence (Battock, Finn, & Barnes, 1990; Nurmikko & Bowsher, 1990) and extent (Battock et al., 1990) of scarring distinguished patients with PHN from herpes zoster patients whose pain did not persist. Because it is likely that scarring is a consequence of a more severe rash during the acute infection, these findings are consistent with the data suggesting that greater rash severity is a risk factor for prolonged pain. It has also been reported that scarring is less severe in PHN patients with predominantly allodynic pain (Rowbotham & Fields, 1989), which suggests that scarring, and perhaps the more severe rash this implies, may be differentially associated with pain quality in herpes zoster and PHN.

Greater Sensory Dysfunction

A fourth risk factor that has been identified by several groups of investigators is the presence of greater sensory deficits in the affected dermatome during acute herpes zoster. Evaluations of sensory dysfunction in the affected dermatome have included clinical assessments of hypesthesia, as well as quantitative sensory testing. Acute herpes zoster patients with greater sensory abnormalities (e.g., hypesthesia, elevated thermal and vibration thresholds) in the affected dermatome, compared to the contralateral unaffected dermatome, were found to be at greater risk for PHN in most (Bruxelle, 1995; Leijon et al., 1993; Noda, Dan, Manabe, & Higa, 1987; Nurmikko, Rasanen, & Hakkinen, 1990) but not all (Haanpää & Nurmikko, 1997) of these studies.

Elevated vibration thresholds *outside* the affected dermatome (i.e., in the hands and feet) have also been found to distinguish herpes zoster patients who developed PHN from those who did not (Baron, Haendler, & Shulte, 1997). It was concluded that these results suggest that a generalized subclinical impairment of A-beta afferent fiber function (i.e., large fiber polyneuropathy) contributes to the development of PHN. Indirect support for this conclusion is provided by the report of an almost twofold greater risk of PHN in patients who developed herpes zoster after the onset of diabetes compared to patients who developed zoster before they developed diabetes (McCulloch, Fraser, & Duncan, 1982); as the authors suggest, diabetic polyneuropathy may render the nerves more susceptible to damage from VZV.

It has also been reported that there is greater sensory dysfunction in the affected dermatome in patients with PHN than in herpes zoster patients whose pain did not persist (Leijon et al., 1993; Nurmikko & Bowsher, 1990; Wildenhoff et al., 1979, 1981). The results of these studies indicate that sensory dysfunction can persist well beyond the acute phase of herpes zoster and that it is a frequent concomitant of prolonged pain.

More Pronounced Immune Response

Greater magnitude and duration of humoral and cell-mediated immune responses in acute herpes zoster patients have been reported to predict prolonged pain (Dan, Higa, Tanaka, & Mori, 1983; Higa et al., 1988, 1992). It is possible that immune responses during acute herpes zoster predict prolonged pain because a more pronounced immune response reflects a more severe acute infection.

Several findings are consistent with this hypothesis. VZV-specific cell-mediated immune responses reach their maximum 1 to 2 weeks after the onset of herpes zoster, which is usually the time of maximal infection (Arvin, Pollard, Rasmussen, & Merigan, 1978). In addition, measures of both humoral and cell-mediated immunity were found to be lower in acyclovir-treated compared to placebo-treated acute zoster patients (Mitchell, Gehrz, & Balfour, 1986); although the group differences were not statistically significant, the dose of acyclovir used (400 mg, five times daily) in this study was only half of what is now accepted as adequate antiviral treatment for herpes zoster. In discussing their results, the investigators suggested that the lower values of the immune response measures may have reflected a reduced "antigenic burden" resulting from the inhibition of viral replication associated with acyclovir treatment (Mitchell et al., 1986). Similarly, antibody titers were found to be significantly lower in children with varicella treated with acyclovir compared to those treated with placebo (Balfour et al., 1990). And in research on two other herpes viruses—herpes simplex virus and Epstein-Barr virus—it has been noted that elevated antibody titers "are thought to reflect the increased production of viral antigens after reactivation" (Glaser & Kiecolt-Glaser, 1994, p. 251).

Presence of a Prodrome

In 70–90% of herpes zoster patients, a prodrome of dermatomal pain begins several days before the appearance of the characteristic rash (Beutner et al., 1995; Dworkin et al., 1998; Rogers & Tindall, 1971). The herpes zoster prodrome is often accompanied by other symptoms—including fatigue, dysesthesias, and headache—and some patients may have these prodromal symptoms in the absence of pain. In three recent studies, the presence of prodromal pain and symptoms was found to be associated with prolonged pain and the development of PHN (Beutner et al., 1995; Choo et al., 1997; Dworkin, Boon, & Griffin, 1995). In future studies of risk factors for PHN, it will be necessary to carefully distinguish prodromal pain from other prodromal symptoms. A series of patients in whom prodromal pain preceded the rash by 7 to more than 100 days has been described (Gilden et al., 1991), and so it will also be important to examine prodrome duration in future research.

Antiviral Therapy

It is well beyond the scope of this chapter to review the literature on the efficacy of antiviral therapy (and other treatments) in acute herpes zoster patients on the development of PHN and on prolonged herpes zoster pain assessed as a continuum. Recent studies have demonstrated that treatment of acute herpes zoster patients with the antiviral agents acyclovir, famciclovir, and valacyclovir reduces both the risk of developing PHN and the overall duration of pain (Beutner et al., 1995; Dworkin et al., 1998; Jackson, Gibbons, Meyer, & Inouye, 1997; Tyring et al., 1995; Wood et al., 1996). In the context of identifying risk factors, the *absence* of antiviral therapy in acute herpes zoster patients may therefore be considered a risk factor for PHN.

Fever

In one study, fever greater than 38°C during acute herpes zoster was reported to predict the development of PHN (Wildenhoff et al., 1981).

Sex

Several investigators have examined whether there is a relationship between the patient's sex and the risk of prolonged pain, and the majority of these studies have found that men and women are equally likely to develop PHN (Beutner et al., 1995; Brown, 1976; Choo et al., 1997; Dworkin et al., 1995, 1998; Fiddian, 1995; Harding et al., 1987; Hope-Simpson, 1975; Wildenhoff et al., 1979, 1981; Wood et al., 1996).

Dermatome

Several investigators have examined the relationship between the specific dermatome affected in acute herpes zoster and the risk of prolonged pain (Burgoon et al., 1957; Choo et al., 1997; De Moragas & Kierland, 1957; Fiddian, 1995; Higa et al., 1997; Hope-Simpson, 1975; Wildenhoff et al., 1979, 1981). Although the results of several of these studies have suggested that the likelihood of prolonged pain is greater in patients with ophthalmic or trigeminal zoster, this relationship has not been found consistently. The results of a recent preliminary analysis of the first 476 herpes zoster patients out of an anticipated total of 2000 suggested that pain was present in a higher proportion of patients with ophthalmic zoster than in patients with zoster in other dermatomes at 6 months after rash onset; the difference between these two groups, however, was not statistically significant (Stillman, 1997). Considered together with the results of previous research, these data suggest that even if future studies demonstrate that PHN is more likely to occur in patients with ophthalmic zoster, it is unlikely that this will be a risk factor with substantial potency (Kraemer et al., 1997).

Psychosocial Risk Factors

The risk factors for PHN discussed to this point have consisted of demographic and biomedical characteristics of patients with acute herpes zoster. It has also been suggested that psychosocial factors might play a role in determining which patients with acute herpes zoster will develop PHN. Pilowsky (1977) proposed that patients who develop PHN are characterized by a constellation of certain premorbid personality traits and stressful life events. Although this hypothesis was based on psychiatric interviews with patients who had suffered from PHN for as long as 15 years, several recent studies have provided data that are consistent with the hypothesis that psychosocial factors

play a role in the development of both acute herpes zoster and PHN. In two studies of risk factors for acute herpes zoster, Schmader and colleagues reported that herpes zoster patients reported increased stressful life events and decreased social support preceding the onset of their infection compared to matched controls who had not had herpes zoster (Schmader, George, Burchett, & Pieper, 1998; Schmader, Studenski, Macmillan, Grufferman, & Cohen, 1990).

The results of other studies have suggested that greater levels of psychological distress (e.g., depression, anxiety) in herpes zoster patients may be risk factors for the development of PHN. In one cross-sectional study, PHN patients had more symptoms of anxiety and rated their past experiences of pain as more intense than herpes zoster patients whose pain had not persisted (Rose, Klenerman, Atchison, & Slade, 1992). In this study, PHN patients had also experienced *fewer* stressful life events in the preceding year, a finding that the authors attributed to the withdrawal from activities that characterizes chronic pain patients. The results of a second cross-sectional study that attempted to identify predictors of PHN "showed a higher frequency of psychopathological impairment" in patients with PHN than in patients with a history of herpes zoster who did not develop chronic pain (Leplow, Lamparter, Risse, & Wassilev, 1990, p. 46). In a recent retrospective study of patients with a history of herpes zoster, those who reported having other diseases and/or psychosocial stress at the onset of their infection were significantly more likely to have PHN, changed daily activities, and lower levels of well-being than patients who reported no other diseases or psychosocial stress at the onset of their infection (Bergbom Engberg, Gröndahl, & Thibom, 1995).

The results of these three studies are consistent with the existence of psychosocial risk factors for PHN. However, the use of cross-sectional and retrospective methods makes it impossible to determine whether psychosocial distress is a risk factor for PHN or whether the *recollection* of such distress being present at the time of the acute herpes zoster infection is simply one of the consequences of PHN. Prospective studies are necessary to determine whether variables that may plausibly be either antecedents or consequences of chronic pain are risk factors (Dworkin, 1991; Kraemer et al., 1997). In a prospective study of a small sample of herpes zoster patients, patients who developed PHN had greater depression, anxiety, and disease conviction and lower life satisfaction during their acute infection than patients who did not develop PHN (R. H. Dworkin et al., 1992). Preliminary analyses of the data from a recent prospective study of a larger sample of acute herpes zoster patients have provided additional evidence that psychosocial factors, including disease conviction and somatosensory amplification, are associated with an increased risk of PHN independently of age and acute pain severity (Dworkin, Cooper, et al., 1997). Two chronic stressors—poor physical health and financial resources—also predicted PHN in this study, but these did not remain significant when age and acute pain severity were controlled (Dworkin, Cooper, et al., 1997). Considered together, the results of the research on the role of psychosocial factors in the natural history of herpes zoster suggest that these factors may play a role in the onset of acute herpes zoster as well as in the development of PHN; this conclusion is consistent with the evidence suggesting that psychosocial factors contribute to the onset and course of other herpes virus infections (Glaser & Kiecolt-Glaser, 1994).

Associations among Risk Factors

There are important unanswered questions about risk factors for PHN that must be addressed in future research. One involves the nature of the associations among the risk factors that have been identified for PHN. For example, it would be valuable to know whether greater acute pain severity and greater rash severity are associated in acute herpes zoster patients. This relationship, however, has been examined in only two studies: In one of these, greater acute pain severity and greater rash duration were associated (Molin, 1969), whereas in the other, acute pain severity and rash severity (assessed by the number of vesicles) were uncorrelated (Bruxelle, 1995). A second important question is whether there are interactions among the risk factors for PHN. For example, is greater acute pain severity a risk factor for PHN in both younger and older patients, or is this relationship limited to only one age group? Similarly, few studies have examined treatment-covariate interactions in the development of PHN. Such analyses have the potential to reveal whether certain herpes zoster patients benefit more from treatment than others. For example, although it has been suggested that intravenous acyclovir has a greater effect on acute pain in older herpes zoster patients than in younger patients (Peterslund et al., 1981), the available data do not directly address whether

antiviral treatment has a significantly greater effect on the risk of PHN in older patients.

Future Directions for Research on Risk Factors for Postherpetic Neuralgia

The most interesting unanswered question about risk factors for PHN is also the one with the longest history—that is, why is older age a risk factor for PHN (Wall, 1993)? It has been hypothesized that age is associated with the development of PHN because older patients have more severe acute herpes zoster infections (Higa et al., 1988, 1997). The results of several studies, however, are not entirely consistent with this hypothesis. Although significant associations between older age and greater rash duration have been reported (Harding et al., 1987; Wildenhoff et al., 1979, 1981), older age is inconsistently associated with greater lesion severity (Higa et al., 1988, 1997) and is not associated with greater acute pain severity (Bamford & Boundy, 1968; Dworkin, Cooper, et al., 1997; Harding et al., 1987). Moreover, the results of several recent studies suggest that age and acute pain severity make independent contributions to predicting which herpes zoster patients develop PHN (Beutner et al., 1995; Dworkin et al., 1998; Dworkin, Cooper, et al., 1997; Wood et al., 1996). To the extent that acute pain severity reflects a more severe acute infection, these findings suggest that the increased risk of PHN in the elderly is not completely accounted for by more severe acute infections and that this increased risk reflects an additional pathophysiological process. Indeed, Hope-Simpson (1967) recognized that although severe acute infections are frequently associated with PHN, even mild cases of zoster are sometimes followed by PHN.

One pathophysiological process that might contribute to an increased risk of PHN in the elderly involves nervous system senescence. The recent report, discussed previously, that large fiber polyneuropathy in acute herpes zoster patients predicts the development of PHN is consistent with this hypothesis and merits continued investigation (Baron et al., 1997). A second process that might explain the increased risk of PHN in the elderly involves immunopathogenesis. It has been hypothesized that autoimmune phenomena and age-associated disturbances in cytokine production, possibly involving cytokine neurotoxicity, may result in nerve damage and contribute to the development of prolonged pain in patients with herpes zoster (Dworkin & Portenoy, 1996; Weksler, 1994). The contribution of immunopathological processes to the development of PHN has not been examined directly; however, this hypothesis is consistent not only with the greater risk of PHN in the elderly but also with several other recent findings, including the existence of pain-free intervals in PHN, evidence of inflammation in patients with well-established PHN, and possibly equivalent risks of PHN in immunocompromised and immunocompetent patients (Dworkin & Johnson, 1998; Dworkin & Portenoy, 1996).

A VULNERABILITY-DIATHESIS-STRESS MODEL OF POSTHERPETIC NEURALGIA

In this section, we will apply the vulnerability-diathesis-stress model of chronic pain presented above to the development of PHN.[1] As discussed previously, the vulnerability component of the model comprises neurobiological and psychosocial predisposing factors. Two of the risk factors for PHN—age and generalized large fiber impairment—can be considered neurobiological predisposing factors. Although older age may reflect psychosocial predisposing factors, as well as neurobiological predisposing factors, the results of a recent study suggested that the effect of age could not be accounted for by increased psychosocial distress in older patients (Dworkin, Cooper, et al., 1997). It is therefore likely that older age reflects neurobiological predisposing factors, and it is possible that subclinical large fiber polyneuropathy explains the greater risk of PHN in the elderly (Baron et al., 1997). Immunopathological processes may also account for the increased risk of PHN in older patients. It is important to note, however, that nervous system senescence and the autoimmune phenomena discussed previously are not mutually exclusive explanations of the relationship between age and PHN.

Several psychosocial risk factors for PHN have been identified and can be considered psychosocial predisposing factors contributing to an individual's vulnerability for PHN. As reviewed previously, symptoms of psychological distress—for example, depression and anxiety—have been found to distinguish patients with PHN from herpes zoster patients whose pain did not persist and to predict

[1] This is a revised and expanded version of a diathesis-stress model of PHN that was proposed recently (Dworkin & Portenoy, 1996).

the development of PHN in several recent cross-sectional and prospective studies. The results of these studies also suggest that somatosensory amplification, disease conviction, and increased pain sensitivity are associated with the development of PHN. Because these variables and acute pain severity have been found to make independent contributions to predicting PHN, they presumably reflect premorbid personality traits and not just the severity of the acute herpes zoster infection.

The diathesis component of the vulnerability-diathesis-stress model of PHN is the severity of the acute herpes zoster infection, and, more precisely, the neural damage that accompanies it. Except for age and the psychosocial variables, the risk factors for PHN that have been identified—acute pain severity, rash severity, sensory dysfunction, more pronounced immune responses, presence of a prodrome, fever, and the absence of antiviral therapy during acute zoster—can all be considered concomitants of a more severe acute herpes zoster infection. Several of these risk factors have been identified by independent groups of investigators, and they provide appreciable support for the conclusion that there is a greater risk of PHN in patients with more severe acute herpes zoster infections. Indeed, over 30 years ago, Hope-Simpson (1967) proposed that patients with more severe acute herpes zoster infections are more likely to develop PHN. More severe acute herpes zoster infections are accompanied by greater neural damage, and it has been proposed that this neural damage contributes prominantly to the development of PHN in patients with herpes zoster (Bennett, 1994; Dworkin & Portenoy, 1996; for recent reviews of the pathophysiology of PHN, see Dworkin & Johnson, 1998; Rowbotham & Fields, 1996).

The stress component of our vulnerability-diathesis-stress model comprises stressful life events and social support and is hypothesized to interact with the diathesis in accounting for the development of PHN. As discussed previously, certain chronic stressors may be risk factors for PHN (Dworkin, Cooper, et al., 1997), and Schmader and colleagues (Schmader et al., 1990, 1998) have reported that various aspects of stress and social support appear to be risk factors for an acute herpes zoster infection. The risk of PHN is hypothesized to increase as both the severity of the neural damage and the severity of the psychosocial stress increase. As illustrated in Figure 16.3, the interaction between the diathesis and stress may have different forms. Preliminary analyses of the data from a prospective study of risk factors for PHN were consistent with the model illustrated in Figure 16.5 in suggesting that psychosocial factors may have a more pronounced effect on the risk of PHN in patients with more severe herpes zoster infections (Dworkin, Cooper, et al., 1997). Note that vulnerability is represented in this figure as a function of age and psychological distress—two risk factors for PHN that reflect putative neurobiological and psychosocial predisposing factors that must be examined in much greater detail in future prospective studies of patients with herpes zoster.

Although it has often been assumed that the diathesis and stress components of diathesis-stress models are independent, individuals with a more severe diathesis may be more likely to incur stressful life events, putting them at even greater risk of developing a disorder (Kendler & Eaves, 1986; Monroe & Simons, 1991; see also Walker, Downey, & Nightingale's [1989] discussion of the conceptual and statistical implications of correlations among

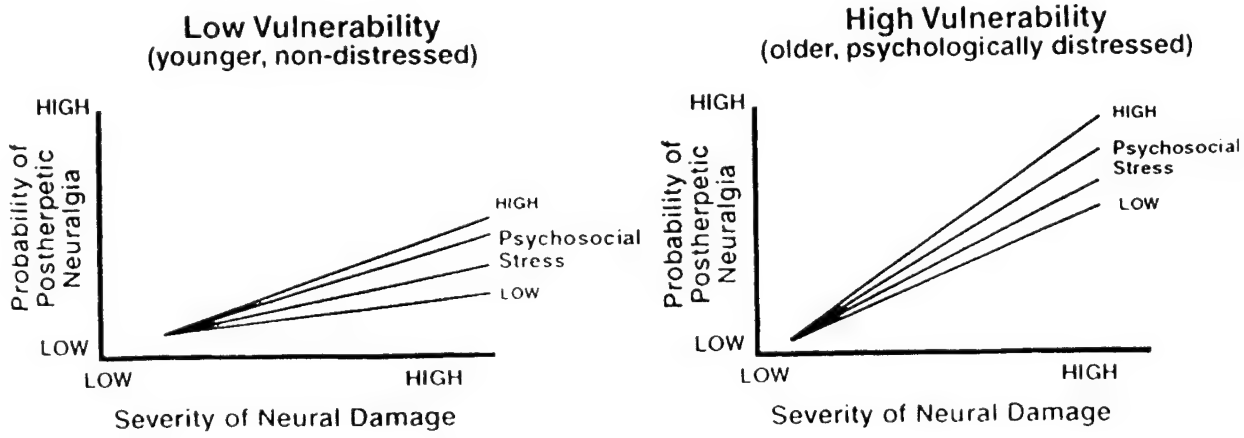

FIGURE 16.5. A vulnerability-diathesis-stress model of postherpetic neuralgia.

risk factors). The model of PHN presented here makes the assumptions that not only are the diathesis for PHN and the psychosocial stress with which it interacts independent, but also that the individual's neurobiological and psychosocial vulnerability is independent of the severity of the diathesis and the level of stress. However, a variety of bidirectional relationships between infectious and behavioral processes have been reported (e.g., Maier, Watkins, & Fleshner, 1994), and it is possible that individuals with more severe acute zoster infections experience increased psychosocial stress as a result of their infections, putting them at even greater risk of prolonged pain. Furthermore, although there is compelling evidence that a decrease in cell-mediated immunity plays an important role in the onset of herpes zoster (Gershon, 1993), the factors accounting for the severity of the acute infection have not been well studied. It is possible that those individuals who have high premorbid psychosocial vulnerability or who are experiencing stressful life events at the onset of their acute herpes zoster have more severe infections, which would put them at even greater risk of PHN. Although such relationships between vulnerability factors, diathesis, and stress do not invalidate the vulnerability–diathesis–stress model, they should be taken into account in future research.

CONCLUSIONS

We suggested previously that current research on chronic pain is characterized by the very same "serious difficulties which suggest the use of the high-risk method" identified by Mednick and McNeil (1968, p. 681)—that is, the difficulties associated with attempting to identify factors that contribute to the development of a disorder in patients who already have the disorder. Prospective studies of acute pain patients and other high-risk groups (e.g., the offspring of chronic pain patients), although requiring a major commitment of time and resources, are needed to address these difficulties. We believe that the goals of research on chronic pain are to understand its pathogenesis, improve its treatment, and prevent its development. To achieve these goals, prospective multivariate studies with testable hypotheses about the interactions among biological, psychological, and social risk factors are needed, and it is our hope that the vulnerability–diathesis–stress model presented in this chapter is a step in this direction.

ACKNOWLEDGMENT

Preparation of this chapter was supported in part by a research grant from the National Institute of Neurological Disorders and Stroke (No. NS-30714).

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